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Hemorrhage in the skin of a newborn

Draft clinical recommendations for discussion by neonatologists and pediatricians

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ABSTRACT

The hemostasis system of newborns is called “developmental hemostasis” and plays an important role in the adaptation of a newborn child to the conditions of the extrauterine environment. Hemorrhages in newborns occur both when individual parts of the hemostasis system (vessels, platelets, coagulation factors) are damaged, and when they are combined. The incidence of cutaneous hemorrhagic syndrome of newborns ranges from 15.0 to 24.9% in neonatal departments of obstetric institutions. According to the type of hemostatic disorders, cutaneous hemorrhagic syndrome is divided into microcirculatory, hematoma and mixed types. The etiopathogenetic classification identifies platelet disorders (qualitative and quantitative) and blood clotting disorders that may be associated with the formation of hematomas and bruises, a combination of these two factors is possible. Cutaneous hemorrhagic syndrome can occur as an isolated one or be accompanied by other manifestations of hemorrhagic syndrome, such as gastrointestinal bleeding, intracranial hemorrhages, retinal bleeding, adrenal hemorrhages, etc. When examining a child with a skin hemorrhage, it is necessary to conduct a thorough examination, collect a hereditary and perinatal anamnesis, perform a general blood test and coagulogram, neurosonography and ultrasound examination of the abdominal cavity, kidneys and adrenal glands to exclude internal bleeding, conduct an oculist examination to exclude retinal hemorrhages. Local treatment of hemorrhages in the skin is not carried out, if disorders of the hemostasis system are detected, then correction of these disorders is carried out, which led to the development of cutaneous hemorrhagic syndrome.

Keywords: skin hemorrhage, newborns, cutaneous hemorrhagic syndrome of newborns, disorders of the hemostasis system of newborns, petechiae

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Кровоизлияние в кожу у новорожденного

Проект клинических рекомендаций для обсуждения специалистами неонатологами и педиатрами

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РЕЗЮМЕ

Система гемостаза новорожденных носит название «гемостаз развития» и играет важную роль в адаптации новорожденного ребенка к условиям внеутробной среды. Кровоизлияния у новорожденных возникают как при повреждении отдельных звеньев системы гемостаза (сосудов, тромбоцитов, факторов коагуляции), так и при их сочетании. Частота кожного геморрагического синдрома новорожденных составляет от 15,0 до 24,9% в отделениях новорожденных родовспомогательных учреждений. Кожный геморрагический синдром по типу нарушений гемостаза подразделяется на микроциркуляторный, гематомный и смешанный типы. Этиопатогенетическая классификация выделяет нарушения со стороны тромбоцитов (качественные и количественные) и нарушения свертываемости крови, которые могут быть связаны с образованием гематом и кровоподтеков, возможно сочетание этих двух факторов. Кожный геморрагический синдром может протекать как изолированный или сопровождаться другими проявлениями геморрагического синдрома, такими как желудочно-кишечные кровотечения, внутричерепные кровоизлияния, ретинальные кровотечения, кровоизлияния в надпочечники и др. При обследовании ребенка с кровоизлиянием в кожу необходимо провести тщательный осмотр, собрать наследственный и перинатальный анамнез, выполнить общий анализ крови и коагулограмму, нейросонографию и ультразвуковое исследование органов брюшной полости, почек и надпочечников для исключения внутренних кровотечений, провести осмотр окулиста для исключения ретинальных кровоизлияний. Местное лечение кровоизлияний в кожу не проводится. Если выявлены расстройства системы гемостаза, то проводится коррекция этих нарушений, которые привели к развитию кожного геморрагического синдрома.

Ключевые слова: кровоизлияние в кожу, новорожденные, кожный геморрагический синдром новорожденных, нарушения системы гемостаза новорожденных, петехии

Как цитировать

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DEFINITION

Hemorrhage in the skin of a newborn is a clinical and hematological syndrome characterized by the occurrence of hemorrhages into the skin and subcutaneous tissue due to disorders in the hemostatic system.

ETIOLOGY AND PATHOGENESIS

The hemostatic system of newborns is referred to as «developmental hemostasis» and plays a significant role in the adaptation of the newborn infant to the conditions of the extrauterine environment. Hemorrhages in newborns occur both as a result of damage to individual components of the hemostatic system (vessels, platelets, coagulation factors) and in cases of their combined disorders [1, 4, 5]. Damage to the vascular component of hemostasis with the development of cutaneous hemorrhagic syndrome occurs during traumatic deliveries, when the umbilical cord is wrapped around the neck (leading to increased pressure in the veins of the scalp), and during pressure fluctuations that occur during the passage of the chest through the birth canal [15]. Disorders of the cellular component of hemostasis lead to the development of petechiae and ecchymoses on the skin and occur with the development of thrombocytopenia and thrombocytopathy. Thrombocytopenia develops as a result of increased platelet destruction or reduced platelet production, and a combination of these two mechanisms is also possible [20]. Thrombocytopathy (disorder of platelet functional activity) is characteristic of all newborns during the first 10–14 days of life and may be exacerbated by perinatal diseases and the use of medicinal products with platelet-inhibiting properties. Thrombocytopenia and thrombocytopathy can be either acquired or hereditary/congenital. Disorders of coagulation hemostasis lead to the development of superficial hematomas and pronounced subcutaneous tissue ecchymoses, and may accompany a number of perinatal conditions (asphyxia, intrauterine infections, sepsis, vitamin K deficiency, etc.) or be hereditary in nature (hemophilia A, hemophilia B, von Willebrand disease, etc.). Involvement of all components of the hemostasis system in the pathological process occurs with the development of disseminated intravascular coagulation (DIC) syndrome, resulting in the simultaneous appearance of all morphological elements of cutaneous bleeding [4, 5, 9, 12, 18].

EPIDEMIOLOGY

Cutaneous hemorrhagic syndrome is diagnosed in 15.0–24.9% of infants managed in departments for neonatal physiology and pathology, presenting predominantly as petechial rash on the face and upper torso, which is considered a consequence of rapid or prolonged labor [5, 6]. In neonatal intensive care units (NICU), petechial rash is observed in 10.2–31.2% of

newborns and ecchymoses in 4.2–22.2% [2, 5]. Cutaneous hemorrhagic syndrome may occur in isolation (45.5%) or be accompanied by other hemorrhagic manifestations (54.5%) — including subaponeurotic and intracranial hemorrhages, gastrointestinal bleeding, retinal hemorrhages, and adrenal hemorrhages. Isolated cutaneous hemorrhagic syndrome manifests at birth in 48.5% of cases, during the early neonatal period in 25.7%, and during the late neonatal period in 25.7%. Cutaneous hemorrhagic syndrome combined with other bleeding manifestations is diagnosed at birth in 56.1% of cases, in the early neonatal period in 24.3%, and in the late neonatal period in 19.6% [6].

FEATURES OF DISEASE CODING ACCORDING TO THE INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD-10)

P54.0 Hemorrhage into the skin of the newborn.

This code is assigned when hemorrhagic elements in the form of petechiae, ecchymoses, bruises, or superficial hematoma are present on the newborn's skin, provided that diseases causing cutaneous hemorrhagic syndrome have been excluded. Code P54.0 provides for the registration of only four manifestations of cutaneous bleeding: petechiae, ecchymoses, bruises, and superficial hematomas.

Comment. *If hemorrhage into the skin is part of the symptom complex of a newborn disease that has its own ICD-10 code (e.g., congenital or transient thrombocytopenia, hemophilia, DIC syndrome, hemorrhagic disease of the newborn, birth trauma, congenital cytomegalovirus infection, sepsis), then hemorrhage into the skin is not coded as a separate diagnosis. In such cases, the type of hemorrhagic manifestations on the skin and subcutaneous tissue and the degree of severity of the clinical manifestations of cutaneous hemorrhagic syndrome are specified when justifying the corresponding diagnosis.*

CLASSIFICATION

Classification of cutaneous hemorrhagic syndrome by type of hemostatic disorder

The microcirculatory (petechial-spotty / bruising) type is characterized by painless, non-tense superficial hemorrhages into the skin and mucous membranes that do not compress surrounding tissues or cause their destruction — presenting as petechiae and bruises. Bleeding occurs with minimal trauma to microvessels, for example, at sites of blood pressure cuff application, sensor placement, or removal of adhesive tape [1].

The hematoma type of bleeding is characterized by massive, deep, tense, and typically painful intradermal hemorrhages and hemorrhages into the subcutaneous tissue, including subgaleal hemorrhage with ecchymoses in the neck area. Spontaneous, post-traumatic, and postoperative hemorrhages are observed, most of which are distinctly delayed in nature, occurring several hours after trauma, intramuscular injections, or other skin punctures [1].

The mixed (microcirculatory-hematoma) type is not merely a simple combination of features of the microcirculatory and hematoma types of bleeding, but rather a specific and interconnected aggregation of them. The classic manifestation of this type of bleeding is DIC syndrome [1].

Etiopathogenetic classification [10]

Platelet component disorders, specifically both quantitative and qualitative platelet abnormalities, are associated with bleeding manifestations, including petechiae and ecchymoses.

Qualitative disorders (thrombocytopathies) include Glanzmann thrombasthenia, Bernard–Soulier syndrome, platelet storage pool defects, and other platelet function deficiencies.

Quantitative disorders (thrombocytopenias)

Quantitative disorders include the following.

A. Congenital thrombocytopenias with reduced platelet production: amegakaryocytic thrombocytopoenia, thrombocytopenia with absent radius (TAR) syndrome, amegakaryocytic thrombocytopenia without limb anomalies, Wiskott–Aldrich syndrome, Chediak–Higashi syndrome, May–Hegglin anomaly, Alport syndrome, and Bernard–Soulier syndrome; infiltrative bone marrow disorders, including congenital leukemia, congenital neuroblastoma, Letterer–Siwe disease, and osteopetrosis.

B. Increased platelet destruction: DIC associated with systemic infection or severe birth asphyxia; localized thromboses (e.g., renal vein thrombosis); necrotizing enterocolitis; maternal eclampsia; Kasabach–Merritt syndrome; systemic infections (bacterial, viral, fungal, and protozoal, both congenital and acquired); immune-mediated thrombocytopenias (neonatal alloimmune thrombocytopenia and neonatal autoimmune thrombocytopenia); and von Willebrand disease (type IIB).

C. Combined reduced production and increased destruction of platelets: infection (congenital TORCH syndrome or acquired bacterial sepsis) and erythroblastosis fetalis.

D. Other causes: exchange transfusion, extracorporeal membrane oxygenation, and polycythemia.

Coagulation disorders that may be associated with the formation of hematomas and ecchymoses

Coagulation disorders associated with the formation of hematomas and ecchymoses include the following.

A. Hereditary coagulation factor deficiencies: X-linked recessive disorders (hemophilia A and B); autosomal dominant disorders (von Willebrand disease); and autosomal recessive disorders (deficiencies of factors XI, VII, V, X, II, XIII, and fibrinogen).

B. Acquired coagulation factor deficiencies: vitamin K deficiency; sepsis/necrotizing enterocolitis; renal vein thrombosis; severe liver disease; and maternal use of medications (vitamin K antagonists, salicylic acid and its derivatives, barbiturates and their derivatives, and hydantoin derivatives).

Combined platelet and coagulation system disorders — simultaneous presence of petechiae, ecchymoses, bruises, and hematomas:

- a) disseminated intravascular coagulation;
- b) liver dysfunction.

CLINICAL MANIFESTATIONS

Cutaneous hemorrhagic syndrome may be isolated or combined, primary or secondary, factors that determine its clinical presentation.

In patients with cutaneous hemorrhages, the clinical picture may consist of isolated cutaneous hemorrhagic syndrome (petechiae, ecchymoses, bruises, and hematomas) or may be accompanied by other hemorrhagic manifestations involving the platelet or coagulation arms of hemostasis. These manifestations do not always present with clinical signs of internal organ involvement. Non-massive, moderate hemorrhages at various sites (intraventricular hemorrhage, retinal hemorrhage, adrenal hemorrhage, subcapsular hepatic hematoma, among others) may follow an asymptomatic course. When an infant presents solely with bleeding symptoms, the underlying cause is most likely a hemostatic disorder or vitamin K deficiency (primary hemorrhagic syndrome). Conversely, when the infant exhibits “non-hemorrhagic” symptoms and signs of neonatal conditions — such as birth trauma, intrauterine infection, birth asphyxia, sepsis, severe hemolytic disease of the newborn, among others — the hemorrhagic syndrome may represent a manifestation or complication of an underlying neonatal disease (secondary hemorrhagic syndrome), warranting individualized clinical evaluation [6].

During follow-up of an infant with cutaneous hemorrhages, jaundice may develop due to hemolysis of red blood cells at the sites of hemorrhage, and hyperbilirubinemia may reach levels requiring phototherapy [6].

During follow-up, anemia may also develop; in such cases, further evaluation is warranted to exclude inter-

nal bleeding, which may remain clinically silent for a period of time (intraventricular hemorrhage, adrenal hemorrhage, subcapsular hepatic hematoma, intestinal bleeding, among others) [6].

DIAGNOSIS

Diagnostic criteria

Hemorrhages into the skin serve as a marker of hemostatic system impairment. Such infants require careful examination and evaluation to determine whether the manifestations of cutaneous bleeding represent a compensatory adaptive response of the neonatal hemostatic system to extrauterine life in the setting of the neonatal thrombophilic phenotype, whether they are the initial presentation of an inherited hemostatic disorder, or whether they reflect an underlying neonatal disease, including immune-mediated thrombocytopenias.

History and presenting complaints

- Obtaining a family and perinatal history is recommended to identify possible hemostatic abnormalities associated with the development of cutaneous hemorrhagic syndrome [3–5, 7, 10, 11, 17, 21, 24]. **Strength of recommendation: B (quality of evidence: 3).**

Comments.

Hereditary risk factors for hemostatic abnormalities associated with the development of cutaneous hemorrhagic syndrome include:

1. A family history of increased bleeding tendency, manifested by easy bruising, epistaxis or gingival bleeding, menorrhagia, or prolonged bleeding from minor cuts.
2. The presence of relatives with confirmed hemostatic disorders.

Prenatal risk factors for hemostatic abnormalities associated with the development of cutaneous hemorrhagic syndrome include:

1. Maternal factors — hypertensive disorders, eclampsia, diabetes mellitus, medication use, infections, production of autoimmune or alloimmune antiplatelet antibodies, and HELLP syndrome.
2. Placental factors — placental abruption, chronic placental insufficiency, and placental vessel thrombosis.

Intrapartum risk factors for hemostatic abnormalities associated with the development of cutaneous hemorrhagic syndrome include: rapid or precipitous labor; labor abnormalities; malpresentation; asynclitic head engagement; deflexed head positions; low transverse station of the sagittal suture; forceps delivery and vacuum extraction; improper execution of obstetric maneuvers; induction/hyperstimulation of labor; and breech presentation.

Neonatal risk factors for hemostatic abnormalities associated with the development of cutaneous hemorrhagic syndrome include: asphyxia, birth trauma, small or large for gestational age, sepsis, necrotizing enterocolitis, polycythemia, cold injury, severe hyperbilirubinemia, severe hemolytic disease of the newborn, perinatal infections, renal vessel thrombosis and other thrombotic conditions, and use of medications that cause thrombocytopenia, thrombocytopathy, or hypocoagulation.

Physical examination

- In a newborn with signs of cutaneous bleeding, a therapeutic visual examination is recommended [4, 5, 9, 21, 22]. **Strength of recommendation: B (quality of evidence: 3).**

Comments. Therapeutic visual examination includes assessment for bleeding manifestations of the microcirculatory and hematoma types: examination of the skin to identify petechiae and ecchymoses, with attention to the cervical and inguinal folds and axillary region; examination of the neck and postauricular areas, where ecchymoses associated with subgaleal hemorrhage may be visualized; inspection of intramuscular injection sites (vitamin K administration) and the hepatitis B vaccination site, with palpation for induration; comparative measurement of thigh circumferences bilaterally, as intermuscular hematomas may occur in hemophilia, with blood gradually tracking into the subcutaneous tissue and ecchymoses appearing on a delayed basis. Examination of the mucous membranes — the conjunctivae, oral mucosa, and vaginal vestibule — should be performed to detect petechiae. Attention should be paid to bloody discharge from the nose, umbilical stump, or vagina, as well as blood-stained fluid obtained via gastric tube or endotracheal tube, noting the color (pink, brown, red) and amount of discharge. Neurological assessment should focus on signs that may indirectly indicate intracranial hemorrhage: separation of cranial sutures in subarachnoid hemorrhage (SAH) and ocular findings in SAH and intraventricular hemorrhage (IVH). Examination of the diaper contents should note the presence of blood streaks or blood in the stool, as well as a pink tint or blood clots in the urine.

During follow-up examination, attention should be paid to the development of signs of posthemorrhagic anemia, which may indicate that the cutaneous hemorrhagic syndrome is part of a combined presentation. Jaundice may appear after 24–48 hours or later (as hemorrhages resolve).

Laboratory diagnostic tests

- In a newborn with cutaneous hemorrhages, a complete blood count with platelet and reticulocyte counts, with follow-up monitoring, is recommended

to detect thrombocytopenia, anemia due to blood loss, and hematologic signs of infectious disease [4, 5, 9, 16, 19, 25]. **Strength of recommendation: B (quality of evidence: 3).**

- In a newborn with pronounced cutaneous hemorrhages, coagulation studies (a screening assessment of the hemostatic system) are recommended if examination reveals one or more hematomas, one or more ecchymoses, or multiple petechiae and ecchymoses extending to the trunk and limbs beyond the presenting part. Coagulation studies should include measurement of fibrinogen levels, activated partial thromboplastin time, prothrombin time, and international normalized ratio to rule out coagulation disorders, including hemorrhagic disease of the newborn [4, 5, 9, 16, 19, 23, 25]. For differential diagnosis of hemorrhagic disease of the newborn, vitamin K1 (phytomenadione 1% emulsion) should be used. **Strength of recommendation: B (quality of evidence: 3).**

Instrumental diagnostic tests

- For all newborns with cutaneous hemorrhagic syndrome of any severity, neurosonography is recommended to assess for intracranial hemorrhage [4–6, 9, 10, 18, 21]. **Strength of recommendation: B (quality of evidence: 3).**
- For all newborns with multiple manifestations of cutaneous hemorrhagic syndrome, comprehensive abdominal ultrasound, including evaluation of the kidneys and adrenal glands, is recommended to rule out internal bleeding [4–6, 9, 10, 18, 21, 23]. **Strength of recommendation: B (quality of evidence: 3).**
- For newborns with cutaneous hemorrhagic syndrome involving the face combined with hemorrhages on the conjunctiva or sclera, ophthalmology consultation is recommended to rule out retinal hemorrhages [4, 5, 8, 13, 14]. **Strength of recommendation: B (quality of evidence: 3).**

TREATMENT

Treatment is required not for the cutaneous hemorrhages themselves, but for the hemostatic disorders that led to the development of cutaneous hemorrhagic syndrome. Therefore, treatment should be targeted according to the nature of the hemostatic abnormalities.

PREVENTION AND FOLLOW-UP, MEDICAL INDICATIONS AND CONTRAINDICATIONS FOR THE USE

In cases of pronounced isolated cutaneous hemorrhagic syndrome of the petechial-bruising type with normal aPTT and PT, hematology consultation is indicated to rule out thrombocytopathies. Assessment of platelet functional activity is advisable after 2 weeks of age, as

a physiological reduction in platelet functional activity is observed in newborns during the first 2 weeks of life.

ORGANIZATION OF MEDICAL CARE

Evaluation of newborns with cutaneous hemorrhagic syndrome is performed in an inpatient setting.

Indications for hospitalization include:

- 1) the presence of pronounced cutaneous hemorrhagic syndrome (hematomas, ecchymoses, abundant petechial-bruising rash on the non-presenting part);
- 2) severe thrombocytopenia regardless of the severity of cutaneous hemorrhagic syndrome;
- 3) transfer to a higher-level facility (after stabilization of the condition, if necessary) for further evaluation and treatment when the facility where the infant was born lacks the capacity to perform the necessary diagnostic tests, consultations, and treatment.

Indications for discharge from the healthcare facility include:

- 1) satisfactory condition;
- 2) stabilization of the infant's condition with no progression of hemorrhagic elements on the skin;
- 3) no other contraindications to discharge.

CONCLUSION

Hemorrhage into the skin of the newborn is a common condition of the neonatal period, affecting up to 25% of newborns. Careful evaluation of cutaneous hemorrhagic manifestations is essential, as they may arise either from transient birth-related events or as a consequence of severe congenital or hereditary diseases. Any manifestations of cutaneous hemorrhagic syndrome warrant a basic coagulation workup. Based on the identified abnormalities in the platelet or coagulation arms of hemostasis, a diagnostic workup should be performed to identify the underlying condition responsible for the cutaneous bleeding.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Respiratory distress in preterm newborns: clinical features and intensive care tactics

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ABSTRACT

Background. Respiratory disorders or respiratory distress are the most common cause of hospitalization of a newborn in the intensive care unit, and this is typical for both full-term and premature infants.

Aim — to determine the priorities of intensive care tactics for respiratory distress in premature newborns of different gestational age by studying the clinical and laboratory features of its course.

Materials and methods. A retrospective observational multicenter study was performed on 155 newborns, who were divided into two conditional groups depending on the gestational age. Group I included 120 premature newborns with a gestational age of up to 34 weeks, and group II included 35 late premature infants (gestational age — 34–36 (6/7) weeks).

Results. Group I showed lower Apgar scores both one minute and 5 minutes after birth. The median score on the Silverman–Andersen scale in the group I was 5 points, which was statistically significantly higher than in the group II (4 points). The severity of multiple organ dysfunction on the nSOFA (Neonatal Sequential Organ Failure Assessment) scale was higher in patients of the I group (3 vs 2; $p=0.006$). The median duration of mechanical ventilation in the I group of patients was significantly higher (263 vs 63 hours; $p=0.006$). Arterial hypotension was registered in the first 24 hours of life in 19 (12.2%) premature infants: 18 (15%) patients in the group I and 1 (2.8%) child — in the group II, the differences were statistically significant ($p=0.04$). Median volume of volumetric load in the first day of life in the group I was 89, and in the group II — 70 ml/kg in day, which was statistically significant. No statistically significant differences were obtained in terms of the level of hourly diuresis and hydrobalance. Diuresis was 3.6–3.1 ml/kg in hour and was within the permissible values. Inotropic-vasopressor support was provided to 45 (29%) premature infants: 40 (33.3%) patients in group I and 5 (14.3%) in group II. The differences were statistically significant ($p=0.02$). In group I, the median of the vasotropy-inotropic index was 11.2 [5; 12.5], in group II — 8.6 [5; 10], the differences are statistically significant ($p=0.03$).

Conclusion. Early premature infants are a more vulnerable group of newborns who have a severe course of respiratory distress, which requires longer respiratory and more intensive hemodynamic support.

Keywords: respiratory distress, newborns, premature infants, respiratory support

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Особенности течения и тактики интенсивной терапии респираторного дистресса у недоношенных новорожденных

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РЕЗЮМЕ

Актуальность. Дыхательные расстройства или респираторный дистресс являются наиболее частой причиной госпитализации новорожденного в отделение реанимации и интенсивной терапии, причем это характерно как для доношенных, так и недоношенных детей.

Цель исследования — определить приоритеты тактики интенсивной терапии респираторного дистресса у недоношенных новорожденных различного гестационного возраста путем изучения клинических и лабораторных особенностей его течения.

Материалы и методы. Выполнено ретроспективное обсервационное мультицентровое исследование 155 новорожденных детей, которые в зависимости от срока гестации были разделены на две условные группы. В I группу вошли 120 недоношенных новорожденных с гестационным возрастом до 34 недель, во II группу — 35 поздних недоношенных детей (срок гестации — 34–36 (6/7) недель).

Результаты. В группе I выявлены более низкие показатели по шкале Апгар как через одну минуту, так и через 5 минут после рождения. Медиана оценки по шкале Сильвермана–Андерсен в I группе составила 5 баллов, что оказалось статистически значимо выше, чем во II группе (4 балла). Оценка степени выраженности полиорганной дисфункции по шкале nSOFA (Neonatal Sequential Organ Failure Assessment) была выше у пациентов I группы (3 vs 2; $p=0,006$). Медиана длительности искусственной вентиляции легких в I группе пациентов была значимо выше (263 vs 63 часов; $p=0,006$). Артериальная гипотензия в первые сутки жизни зарегистрирована у 19 (12,2%) недоношенных детей: 18 (15%) пациентов в I группе и один (2,8%) ребенок — во II группе, различия были статистически значимыми ($p=0,04$). Медиана объема вolemической нагрузки в первые сутки жизни в I группе составила 89, а во II — 70 мл/кг в сутки, что явилось статистически значимым. По уровню почасового диуреза и гидробаланса статистически значимых различий не получено. Диурез составил 3,6–3,1 мл/кг в час и находился в пределах допустимых значений.

Инотропно-вазопрессорную поддержку проводили 45 (29%) недоношенным детям: 40 (33,3%) пациентам I группы и 5 (14,3%) — II, выявленные различия статистически значимы ($p=0,02$). В I группе медиана вазотропно-инотропного индекса составила 11,2 [5; 12,5], во II — 8,6 [5; 10], различия статистически значимы ($p=0,03$).

Вывод. Ранние недоношенные дети являются более уязвимой группой новорожденных, у которых отмечается тяжелое течение респираторного дистресса, что требует более длительной респираторной и более интенсивной гемодинамической поддержки.

Ключевые слова: респираторный дистресс, новорожденные, недоношенные, респираторная поддержка

Как цитировать

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INTRODUCTION

A key aspect of the newborn's transition to extra-uterine life is the adaptation of the respiratory system. A broad range of pathological conditions involving the respiratory, circulatory, and central nervous systems, as well as metabolic disturbances and other factors, can lead to the development and progression of respiratory disorders. Respiratory disorders, or respiratory distress, are the most common reason for neonatal admission to the intensive care unit, a finding that applies to both term and preterm infants [9]. Approximately 15% of term newborns and 29% of preterm newborns are admitted to intensive care units due to various conditions associated with respiratory distress [7, 13].

Among all newborns, late preterm infants at 34–37 weeks' gestation account for approximately 70–75%, and their numbers have been steadily increasing in recent years [4].

The clinical signs of respiratory distress include tachypnea, nasal flaring, retractions, grunting, and cyanosis [3].

The most common causes of respiratory distress in newborns are respiratory distress syndrome (RDS), sepsis, intra-amniotic infection, meconium aspiration syndrome (MAS), transient tachypnea of the newborn (TTN), neonatal pneumonia, and asphyxia [3, 15].

Although neonatal respiratory failure is treatable in most cases, severe cases require a rational diagnostic and therapeutic approach to optimize outcomes and minimize morbidity.

Newborns with respiratory distress often require prolonged intensive respiratory support, leading to lon-

ger stays in both the intensive care unit and the hospital overall. This is associated with adverse short- and long-term consequences that necessitate long-term pediatric follow-up [5, 11].

To date, the clinical and laboratory characteristics of preterm infants with respiratory failure across different gestational ages remain insufficiently studied. Furthermore, no comprehensive intensive care management protocol has been established, hindering the development of personalized treatment approaches for these patients.

AIM

The aim of this study was to establish priorities for intensive care strategies in managing respiratory distress in preterm infants across different gestational ages by analyzing the clinical and laboratory features of its course.

MATERIALS AND METHODS

This retrospective observational multicenter study was conducted at the neonatal intensive care units of the Perinatal Centers of Leningrad Regional Clinical Hospital and Voronezh Regional Clinical Hospital No. 1.

A total of 155 newborns were enrolled and stratified into two groups based on gestational age. Group I consisted of 120 preterm infants with a gestational age of less than 34 weeks, while Group II included 35 late preterm infants with a gestational age of 34 to 36 weeks and 6 days. The characteristics of the study population are summarized in Table 1.

Table 1. General characteristics of early and late preterm infants

Таблица 1. Общая характеристика ранних и поздних недоношенных

Показатели / Parameters	I группа / I group (n=120)	II группа / II group (n=35)	p (U-тест Манна–Уитни) / (Mann–Whitney U test)
Масса тела при рождении, г / Body mass at birth, g	1322 [900; 1680]	2155 [1870; 2390]	0,00001
Рост, см / Height, cm	39 [35; 42]	46 [44; 47]	0,00001
Оценка по шкале Апгар на 1-й минуте, баллы / Apgar score at 1 minute, points	5 [4; 6]	6 [5; 7]	0,0003
Оценка по шкале Апгар на 5-й минуте, баллы / Apgar score at 5 th minutes, points	6 [6; 7]	7 [6; 8]	0,0004
Срок гестации, недели / Gestation period, weeks	30 [27; 32]	35 [34; 35]	0,00001
Оценка по Сильверману-Андерсен, баллы / Silverman-Andersen score, points	5 [3; 7]	4 [3; 5]	0,001
Оценка по nSOFA, баллы / nSOFA score, points	3 [0; 5]	2 [0; 4]	0,006
Длительность искусственной вентиляции легких, часы / Duration of mechanical ventilation, hours	263 [14; 338]	63 [2; 66]	0,006
Длительность лечения в отделении реанимации и интенсивной терапии новорожденных, дни / Duration of treatment in the neonatal intensive care unit, days	20 [6; 32]	8 [4; 9]	0,00001

Inclusion criteria:

- 1) gestational age under 37 weeks;
- 2) presence of respiratory distress within the first 24 hours of life;
- 3) need for supplemental oxygen or mechanical ventilation.

Exclusion criteria:

- 1) congenital central nervous system malformations;
- 2) confirmed genetic disorders;
- 3) diabetic fetopathy;
- 4) congenital anomalies requiring emergency surgical intervention.

The study was approved by the local ethics committee of St. Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation (Protocol No. 1/3, January 21, 2019).

Initial stabilization in the delivery room was provided to all newborns with respiratory disturbances presenting as ineffective spontaneous breathing [2], in accordance with the methodological letter of the Ministry of Health of the Russian Federation No. 15-4/10/2-3204 (April 21, 2010)¹.

Noninvasive respiratory support was initiated when the Silverman–Andersen score exceeded 4 points. If pronounced oxygen dependence ($\text{FiO}_2 > 0.4$) and signs of respiratory failure persisted for 30 minutes after birth, exogenous surfactant (Curosurf, Chiesi, Italy) was administered endotracheally at a dose of 200 mg/kg.

While continuing noninvasive respiratory support with the Stephan Reanimator F120 Mobile device (Stephan, Germany), the newborn was transported from the delivery room to the neonatal intensive care unit in a transport incubator (ITN-01, Ural Optical and Mechanical Plant named after E.S. Yalamov Production Association, Russia).

In the neonatal intensive care unit, noninvasive respiratory support was continued. If oxygen dependence ($\text{FiO}_2 > 0.4$) was required to achieve target transcutaneous oxygen saturation ($\text{SpO}_2 = 90\text{--}94\%$), or if refractory respiratory acidosis ($\text{pH} \leq 7.20$) developed, the infant was transitioned to mechanical ventilation. Syndromic therapy was also provided.

Organ dysfunction severity was assessed using the nSOFA (Neonatal Sequential Organ Failure Assessment) score [19], with the worst values recorded during the study period used for analysis.

To evaluate the invasiveness of fluid therapy and hemodynamic support aimed at maintaining optimal cardiac output, the total volume of fluid administered, fluid balance, and the vasoactive-inotropic score were analyzed [8].

Based on data from the newborn's developmental history and inpatient medical records, 143 parameters were analyzed, encompassing medical history, clinical, laboratory, and instrumental findings, intensive care interventions, and disease outcomes.

Statistical analysis. Normality of the data was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. As the distribution of the primary data deviated from normal, quantitative variables are reported as medians (Me) with interquartile ranges (LQ–HQ). Differences in ordinal and scaled values were evaluated using the Wilcoxon test, with the Z-value reported. Spearman's rank correlation coefficient was used. The level of statistical significance was set at $p < 0.05$.

RESULTS

Comparison of Apgar scores revealed statistically significant differences in median values between groups both at 1 and 5 minutes, with higher scores observed in Group II (late preterm infants). An Apgar score of ≤ 3 at 5 minutes, indicative of severe intrapartum asphyxia, was recorded in 3 (2.5%) infants in the early preterm group. No such cases occurred in Group II, though this difference was not statistically significant.

The median Silverman–Andersen score was significantly higher in Group I than in Group II (5 vs. 4 points). Similar findings were observed for multiorgan dysfunction severity assessed by the nSOFA score (3 vs. 2; $p = 0.006$), reflecting more severe clinical status in Group I patients.

The median duration of mechanical ventilation was 263 hours in Group I compared with 63 hours in Group II ($p < 0.05$). Mechanical ventilation lasting ≥ 168 hours occurred in 48 cases, accounting for 31% of all preterm newborns with respiratory distress.

Prolonged mechanical ventilation was observed in 45 (37.5%) cases in Group I versus 3 (8.6%) in Group II ($p = 0.0005$) (Table 2). Length of stay in the neonatal intensive care unit was also significantly longer in Group I (20 vs. 8 days). Clinical and laboratory characteristics of newborns during the first 24 hours of NICU treatment are presented in Table 2.

SpO_2 and heart rate did not differ significantly between groups. Analysis of blood pressure showed that systolic, diastolic, and mean arterial pressures were significantly lower in Group I than in Group II.

Arterial hypotension during the first 24 hours of life occurred in 19 (12.2%) preterm infants: 18 (15%) in Group I versus 1 (2.8%) in Group II ($p = 0.04$). No significant differences were observed between groups in blood gas parameters, acid–base status, hemoglobin, leukocyte or platelet counts, C reactive protein, or procalcitonin.

Correlation analysis revealed no significant associations between lactate levels and nSOFA score, blood

¹ Letter of the Ministry of Health and Social Development of the Russian Federation No. 15 4/10/2 3204 dated April 21, 2010, "Primary and Resuscitation Care for Newborn Infants." Available at: <https://docs.cntd.ru/document/902232603> (accessed May 30, 2025). (In Russian.)

pressure, or urine output. However, a negative correlation was found between lactate levels and pH ($R=-0.24$; $p=0.007$), as well as between lactate concentration and umbilical cord blood bicarbonate ($R=-0.35$; $p<0.001$).

On the first day of NICU treatment, protein levels were significantly lower in Group I than in Group II.

Alanine aminotransferase (ALT) levels were significantly lower in Group I. ALT above the reference range (>31 U/L) occurred in 20 (16.6%) cases in Group I versus 7 (20%) in Group II, a non significant difference.

Positive correlations were found between ALT levels and nSOFA score ($R=0.25$; $p=0.002$), as well as between ALT concentration and lactate ($R=0.3$; $p=0.001$). Negative correlations were identified between lactate and bicarbonate ($R=-0.3$; $p=0.007$), and between the

degree of hyperlactatemia and urine output during the first 24 hours ($R=-0.17$; $p=0.02$), confirming lactate's role as a marker of hypoperfusion.

No significant differences in aspartate aminotransferase levels were observed between groups; however, values exceeding the upper reference limit (>75 U/L) were noted in 6 (5%) patients in Group I and 3 (8.6%) in Group II ($p=0.3$).

The main intensive care interventions are summarized in Table 3. Median fluid loading volume during the first 24 hours of life was significantly higher in Group I than in Group II (89 vs. 70 mL/kg/day). No significant differences were found in hourly urine output or fluid balance. Urine output ranged from 3.6 to 3.1 mL/kg/h, remaining within acceptable limits.

Table 2. Clinical and laboratory characteristics of newborns on the first day of intensive care unit treatment

Таблица 2. Клинико-лабораторные характеристики новорожденных в первые сутки лечения в отделении реанимации и интенсивной терапии

Параметры / Parameters	I группа / I group (n=120)	II группа / II group (n=35)	p
SpO ₂ в 1-й день жизни, % / SpO ₂ on the 1 st day of life, %	94 [92; 96]	95 [93; 98]	0,1
Частота сердечных сокращений в 1-й день жизни, уд./мин / Heart rate on the 1 st day of life, beats/min	148 [137; 158]	142 [130; 152]	0,07
Систолическое артериальное давление в 1-й день жизни, мм рт. ст. / Systolic blood pressure on the 1 st day of life, mmHg	54 [48; 58]	59 [54; 64]	0,0003
Диастолическое артериальное давление в 1-й день жизни, мм рт. ст. / Diastolic blood pressure on the 1 st day of life, mmHg	29 [24; 33]	33 [28; 36]	0,006
Среднее артериальное давление в 1-й день жизни, мм рт. ст. / Mean arterial pressure on the 1 st day of life, mmHg	37 [32; 42]	41 [37; 45]	0,005
pH венозной крови в 1-й день жизни / Venous blood pH on the 1 st day of life	7,34 [7,31; 7,39]	7,35 [7,3; 7,4]	0,8
pO ₂ венозной крови в 1-й день жизни, мм рт. ст. / Venous blood pO ₂ on the 1 st day of life, mmHg	56 [42; 59]	62 [43; 70]	0,2
pCO ₂ венозной крови в 1-й день жизни, мм рт. ст. / Venous blood pCO ₂ on the 1 st day of life, mmHg	32,2 [27,8; 36,4]	31 [26; 37]	0,3
HCO ₃ венозной крови в 1-й день жизни, ммоль/л / Venous blood HCO ₃ on the 1 st day of life, mmol/l	19 [17; 20]	18 [17; 20]	0,9
BE венозной крови в 1-й день жизни, ммоль/л / Venous blood base excess on the 1 st day of life, mmol/l	7,5 [5,2; 9,6]	6,9 [5,8; 8,6]	0,6
Лактат венозной крови в 1-й день жизни, ммоль/л / Venous blood lactate on the 1 st day of life, mmol/l	3,4 [2,2; 3,9]	3,7 [2,4; 5,2]	0,2
Гемоглобин в 1-й день, г/л / Hemoglobin on the 1 st day of life, g/l	169 [146; 190]	173 [159; 201]	0,4
Лейкоциты в 1-й день жизни, $\times 10^9$ /л / Leukocytes on the 1 st day of life, $\times 10^9$ /l	13,6 [8,6; 15,4]	13,5 [11; 16]	0,1
Тромбоциты в 1-й день жизни, $\times 10^9$ /л / Platelets on the 1 st day of life, $\times 10^9$ /l	244 [179; 289]	299 [201; 389]	0,02
C-реактивный белок в 1-й день жизни, мг/л / C-reactive protein on the 1 st day of life, mg/l	2,65 [0,15; 3]	2,1 [0,1; 2,73]	0,6
Прокальцитонин в 1-й день жизни, нг/мл / Procalcitonin test on the 1 st day of life, ng/ml	2,8 [0,12; 1,5]	16,8 [0,56; 33]	0,2
Общий белок в 1-й день жизни, г/л / Total protein on the 1 st day of life, g/l	44,5 [38; 50]	52,6 [46; 58]	0,00003
Аланинаминотрансфераза в 1-й день жизни, ЕД/л / Alanine aminotransferase on the 1 st day of life, U/l	16,2 [5; 17,5]	25 [8; 28]	0,01
Аспартатаминотрансфераза в 1-й день жизни, ЕД/л / Aspartate aminotransferase on the 1 st day of life, U/l	60 [33; 69]	67 [32; 87]	0,2

Inotropic-vasopressor support was administered to 45 (29%) preterm infants: 40 (33.3%) in Group I versus 5 (14.3%) in Group II ($p=0.02$). The median vasoactive-inotropic score was 11.2 [5; 12.5] in Group I compared with 8.6 [5; 10] in Group II ($p=0.03$). Positive correlations were found between VIS and peak inspiratory pressure ($R=0.2$; $p=0.02$), and between VIS and nSOFA score ($R=0.53$; $p<0.001$).

Median peak inspiratory pressure was 19 and 17 cm H₂O in Group I and Group II, respectively, and positive end expiratory pressure was 6.2 and 5.8 cm H₂O, with no significant differences between groups. The fraction of inspired oxygen during the first 24 hours of therapy was maintained at safe levels: a median of 0.3 in Group I versus 0.28 in Group II ($p<0.05$; Table 3).

The oxygenation index on the first day of life was significantly lower in Group I than in Group II (318 vs. 358), suggesting more severe respiratory distress;

however, no correlation was observed between the oxygenation index and Silverman–Andersen score.

Table 4 presents the characteristics of respiratory support in the delivery room. Noninvasive respiratory support (NIPPV and CPAP) was used significantly more frequently in Group I than in Group II, as was invasive respiratory support ($p=0.03$).

An analysis of respiratory support in the neonatal intensive care unit is presented in Table 5.

No significant differences were found between the groups in the use of various respiratory support modalities.

DISCUSSION

The results of this study demonstrate a relationship between gestational age and the frequency and severity of respiratory distress in newborns. The most severe course of respiratory distress was observed in

Table 3. Intensive care measures in newborns on the first day of intensive care unit treatment

Таблица 3. Мероприятия интенсивной терапии у новорожденных в первые сутки лечения в отделении реанимации и интенсивной терапии

Параметры / Parameters	I группа I group Me [LQ; UQ] (n=120)	II группа II group Me [LQ; UQ] (n=35)	p
Интенсивная терапия в 1-й день, мл/кг / Total fluid intake on day 1, ml/kg	89 [80; 98]	70 [60; 80]	0,0001
Диурез в 1-й день, мл/кг / Urine output on day 1, ml/kg	3,6 [2,3; 4,5]	3,1 [2; 4,1]	0,11
Гидробаланс в 1-й день % / Fluid balance on day 1, %	61 [13; 100]	65,7 [29; 100]	0,5
Катехоламиновый индекс, баллы / Catecholamine index, points	11,2 [5; 12,5]	8,6 [5; 10]	0,05
FiO ₂ в 1-й день жизни, % / FiO ₂ on the 1st day of life, %	0,3 [0,25; 0,4]	0,28 [0,21; 0,3]	0,037
PIP в 1-й день жизни, мм рт. ст. / PIP on the 1st day of life, mmHg	19 [18; 22]	17 [12; 21]	0,11
PEEP в 1-й день жизни, мм рт. ст. / PEEP on the 1st day of life, mmHg	6,2 [5,5; 6]	5,8 [6; 6]	0,6
Дотация энергетических субстратов, кКал / Energy substrate supplementation, kcal/kg/day	38 [28; 49]	42,4 [28; 51]	0,7
Индекс оксигенации в 1-й день жизни / Oxygenation index on the 1st day of life	318 [260; 368]	358 [300; 447]	0,02

Note: FiO₂ — fraction of inspired oxygen; PIP — positive inspiration pressure; PEEP — positive end-expiratory pressure.

Table 4. Respiratory support in the delivery room

Таблица 4. Респираторная поддержка в родильном зале

Вид респираторной поддержки / Type of respiratory support	I группа / I group (n=120)	II группа / II group (n=35)	P-значение (точный тест Фишера) / p-value (Fisher's exact test)
nCPAP / nCPAP	33 (27,5%)	14 (40%)	0,1
NIPPV / NIPPV	18 (15%)	1 (2,8%)	0,04
CPAP / CPAP	6 (5%)	7 (20%)	0,01
Неинвазивная респираторная поддержка, всего / Non-invasive respiratory support, total	57 (47,5%)	22 (62,9%)	0,08
Assist Control	18 (15%)	4 (11,4%)	0,4
SIMV / SIMV	40 (33,3%)	6 (17,1%)	0,04
Инвазивная респираторная поддержка, всего / Invasive respiratory support, total	58 (48,3%)	10 (28,6%)	0,03

Note: nCPAP — nasal Continuous Positive Airway Pressure; nIPPV — Noninvasive Positive Pressure Ventilation; CPAP — Continuous Positive Airway Pressure.

Table 5. Respiratory support in the neonatal intensive care unit

Таблица 5. Респираторная поддержка в отделении реанимации и интенсивной терапии новорожденных

Вид респираторной поддержки / Type of respiratory support	I группа / I group (n=120)	II группа / II group (n=35)	p-значение (точный тест Фишера) / p-value (Fisher's exact test)
NCPAP / NCPAP	7	1	0,4
NIPPV / NIPPV	25	10	0,3
CPAP / CPAP	10	6	0,1
Неинвазивная респираторная поддержка, всего / Non-invasive respiratory support, total	42	17	0,1
Assist Control	20	5	0,5
SIMV / SIMV	46	10	0,2
Инвазивная респираторная поддержка, всего / Invasive respiratory support, total	66	15	0,14

Note: nCPAP — nasal Continuous Positive Airway Pressure; nIPPV — Noninvasive Positive Pressure Ventilation; CPAP — Continuous Positive Airway Pressure.

early preterm infants, as reflected by higher nSOFA organ dysfunction scores; these infants also required longer mechanical ventilation and NICU stays. These findings support stratifying early preterm newborns into the high risk group for severe disease. In contrast to some researchers [14], we believe that focusing exclusively on late preterm infants is insufficient.

Apgar scores were significantly lower in the early preterm group than in late preterm infants. This aligns with reports that low birth weight and low Apgar scores at 1 and 5 minutes are most often associated with the development of severe respiratory disorders [6].

Several clinical scales are used to assess the severity of respiratory distress in newborns. The most widely cited is the Silverman–Andersen score [18]. We found that a high score (>4 points) is associated with increased venous carbon dioxide tension, complications, and prolonged invasive respiratory support. Other authors, like us, consider a score of ≥ 5 points a reliable predictor of the need for respiratory support [10].

It has been shown that predictors of bronchopulmonary dysplasia in newborns with respiratory distress syndrome include not only low birth weight and gestational age <32 weeks, but also a total duration of oxygen therapy exceeding 10 days [17].

The need for respiratory support in term newborns is also highly variable, depending on the frequency of respiratory distress across different gestational ages. The highest incidence was observed at 37 weeks' gestation (1.7%), gradually decreasing to a minimum at 39 weeks (0.6%), followed by a slight increase at 40 weeks (0.7%) and 41 weeks (0.8%) [12].

Venous carbon dioxide levels were extremely low in all newborns, indicating excessive respiratory support in most cases, occurring alongside compensatory tachypnea driven by base deficit and the unique metabolic profile of preterm infants.

Low birth weight and low gestational age are the main risk factors for adverse neonatal outcomes, particularly in hospitals in low income countries with limited staff training and resources. Preterm infants with extremely low birth weight represent a particularly high risk group, especially when complicated by severe infections or sepsis. Respiratory distress was most severe in the early preterm group, accompanied by arterial hypotension requiring pharmacological hemodynamic support. These infants also required longer mechanical ventilation, which in turn prolonged NICU stays [16]. In most cases, particularly in term newborns, the disease had a favorable course and, in the majority (47%), resulted in complete recovery [1].

CONCLUSIONS

1. Early preterm newborns have a more severe course of respiratory distress, reflected by higher nSOFA scores, longer mechanical ventilation requirements, and higher NICU admission rates.

2. Despite comparable respiratory and nutritional support strategies between the groups, early preterm newborns are more prone to arterial hypotension requiring pharmacological hemodynamic support.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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The effect of exogenous ganglioside GM1 on the expression of apoptotic genes in the hippocampus in a model of chronic alcohol intoxication

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ABSTRACT

Background. Ganglioside GM1 is of interest as a promising compound with nootropic properties for the correction of damage to the central nervous system, particularly in neurodegenerative processes.

Aim. To study the effect of exogenous ganglioside GM1 on the expression of key apoptosis regulatory genes (caspase-1, caspase-3, *Bcl-2*, *BAX*) in the hippocampus of mice under conditions of chronic alcohol intoxication, which acts as a catalyst for neurodegeneration.

Materials and methods. An experiment was conducted on 40 male BALB/c mice divided into 4 groups: intact control, a chronic alcohol intoxication model (intragastric administration of ethanol according to a stepwise schedule for 47 days), and two groups receiving ethanol in combination with GM1 at doses of 10 and 30 mg/kg. The mRNA levels of target genes in the hippocampus were analyzed using quantitative real-time reverse transcription polymerase chain reaction. Statistical data processing was performed using a two-way ANOVA.

Results. Caspase-1 mRNA levels were non-significantly increased in all ethanol-treated groups. Caspase-3 mRNA levels were significantly ($p < 0.05$) increased only in the GM1 30 mg/kg group compared to the model group. *BAX* mRNA levels remained unchanged. *Bcl-2* gene expression in the control group was statistically significantly different from all experimental groups.

Conclusions. The expected effect of GM1 ganglioside at the transcriptional level, namely protection against neurodegeneration, was not confirmed in this model. The key result was the identification of a potential pro-apoptotic effect of a high dose of GM1 (30 mg/kg), manifested by a statistically significant increase in caspase-3 gene expression.

Keywords: alcohol intoxication, monosialotetrahexosylganglioside, alcohol-induced disorders, hippocampus, apoptosis, ganglioside GM1, neuroprotection, quantitative real-time reverse transcription polymerase chain reaction, mRNA, caspase-1, caspase-3, *BAX*, *Bcl-2*

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Влияние экзогенного ганглиозида GM1 на экспрессию апоптотических генов в гиппокампе на модели хронической алкогольной интоксикации

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РЕЗЮМЕ

Актуальность. Ганглиозид GM1 представляет интерес как перспективное соединение с ноотропными свойствами для коррекции повреждений центральной нервной системы, в частности при нейродегенеративных процессах.

Цель. Изучить влияние экзогенного ганглиозида GM1 на экспрессию ключевых генов-регуляторов апоптоза (каспазы-1, каспаза-3, *Bcl-2*, *BAX*) в гиппокампе мышей в условиях хронической алкогольной интоксикации, выступающей в роли катализатора нейродегенерации.

Проведен эксперимент на 40 самцах мышей BALB/c, разделенных на четыре группы: интактный контроль, модель хронической алкогольной интоксикации (внутрижелудочное введение этанола по ступенчатой схеме в течение 47 дней) и две группы, получавшие этанол в сочетании с GM1 в дозах 10 и 30 мг/кг. Уровень мРНК целевых генов в гиппокампе анализировали методом количественной полимеразной цепной реакции с обратной транскрипцией в реальном времени. Статистическую обработку данных проводили с использованием двухфакторного дисперсионного анализа (two-way ANOVA).

Результаты. Уровень мРНК каспазы-1 статистически незначимо повышен во всех группах, получавших этанол. Уровень мРНК каспазы-3 статистически значимо ($p < 0,05$) повышен только в группе GM1 30 мг/кг по сравнению с модельной группой. Уровень мРНК гена *BAX* оставался без значимых изменений. Экспрессия гена *Bcl-2* в контрольной группе статистически значимо отличалась от всех опытных групп.

Выводы. В рамках данной модели не подтвержден ожидаемый эффект ганглиозида GM1 на транскрипционном уровне, заключающийся в защите от нейродегенерации. Ключевым результатом служит выявление потенциального проапоптотического действия высокой дозы GM1 (30 мг/кг), проявляющегося в статистически значимом повышении экспрессии гена каспазы-3.

Ключевые слова: алкогольная интоксикация, моносиалотетрагексозилганглиозид, алкоголь-индуцированные нарушения, гиппокамп, апоптоз, ганглиозид GM1, нейропротекция, количественная полимеразная цепная реакция с обратной транскрипцией в реальном времени, мРНК, каспаза-1, каспаза-3, *BAX*, *Bcl-2*

Как цитировать

Мавлиханова А.А., Катаев В.А., Гизатуллин Т.Р., Цыган В.Н. Влияние экзогенного ганглиозида GM1 на экспрессию апоптотических генов в гиппокампе на модели хронической алкогольной интоксикации. *Педиатр.* 2025;16(5):25–32. <https://doi.org/10.56871/PED.2025.82.71.003>.

INTRODUCTION

Exogenous monosialotetrahexosylganglioside (hereinafter ganglioside GM1) represents a promising neuroprotective compound of considerable interest. Being a naturally occurring and one of the most abundant gangliosides in the neuronal membranes of the central nervous system, it is obtained as a pharmaceutical agent through extraction from animal brain tissue [1–3]. Its pharmacological value stems from a broad range of neurotropic effects, chief among which is its neurotrophic action, reflected in the potentiation of signaling cascades involving brain trophic factors [1, 4]. The established neuroprotective potential has driven scientific interest in its application for various neurodegenerative conditions, including Parkinson's and Alzheimer's diseases [5–7]. Given its ability to protect neurons from damage and support their function, ganglioside GM1 is considered in the present study a promising candidate for counteracting toxic injury to the hippocampus. A model of chronic ethanol intoxication was used as a well-characterized pathological insult that leads to persistent cognitive impairment and neurodegeneration. This model allows for the study of mechanisms underlying central nervous system damage, a key feature of which is progressive decline in memory and learning functions associated with degenerative changes in the hippocampus.

Activation of programmed cell death is considered a central event in the pathogenesis of ethanol-induced neuronal injury [8, 9]. Accumulating evidence implicates various forms of apoptosis and pyroptosis in hippocampal degeneration [10–12]. However, the contribution of specific molecular cascades, such as caspase-dependent pathways and the system of mitochondrial apoptosis regulators (Bcl-2, BAX), requires further elucidation, which is necessary for the development of targeted neuroprotective strategies [13–20].

As a natural constituent of neuronal membranes, ganglioside GM1 plays a key role in maintaining neuroplasticity and cellular resistance to apoptosis. Existing evidence supports its capacity to modulate trophic factors and suppress oxidative stress [4, 6]. However, the mechanisms underlying its beneficial effects on apoptotic markers and cognitive function under neurotoxic conditions remain insufficiently understood.

AIM

The aim of the present study was to assess the effect of ganglioside GM1 on the transcriptional activity of genes involved in regulating the mitochondrial apoptotic pathway (*BAX*, *Bcl-2*) and on caspase activity (caspase-1, caspase-3). These parameters were evaluated in the hippocampus under conditions of ethanol-induced neurotoxicity.

MATERIALS AND METHODS

A total of 40 adult male BALB/c mice weighing 25–30 g were used in the experiment. The animals were housed in a vivarium under standard conditions, including a natural light cycle, a temperature of 20–24 °C, humidity of 50–60%, and free access to water and food. All procedures were performed in accordance with international guidelines and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, and the study protocol was approved by the local ethics committee prior to the initiation of the experiment.

After one week of acclimatization, the animals were randomly assigned to four groups of 10 animals each:

- 1) the control (intact) group that received physiological saline *per os*;
- 2) the model group that underwent chronic alcohol intoxication according to the protocol;
- 3) the GM1 10 mg/kg group (therapeutic, low dose) that received ethanol according to the protocol plus ganglioside GM1 at 10 mg/kg;
- 4) the GM1 30 mg/kg group (therapeutic, high dose) that received ethanol according to the protocol plus GM1 at 30 mg/kg.

Chronic alcohol intoxication was induced by daily intragastric administration of ethanol (97%, Shanghai Aladdin Reagent Company) using a stepwise regimen over 47 days, with progressively increasing concentrations from 5% to 45% (5% solution for 5 days, 15% for 5 days, 25% for 10 days, 35% for 10 days, and 45% for 17 days). The volume of administered solution was adjusted based on individual body weight.

The ganglioside GM1 preparation (Heilongjiang Harbin Medical University Pharmaceutical Co., Ltd.) was dissolved in physiological saline and administered intraperitoneally at the specified doses throughout the experimental period. The control group received equivalent volumes of physiological saline.

After 47 days, the experiment was terminated early due to pronounced signs of deterioration in animals from the model and GM1 10 mg/kg groups. Euthanasia was performed in accordance with the recommendations of the Federation of European Laboratory Animal Science Associations (FELASA). Following induction of deep anesthesia by intraperitoneal administration of 1% sodium pentobarbital, transcardiac perfusion was performed. First, 20–25 mL of physiological saline was injected through the left ventricle to remove blood, which was drained through an incision in the right atrium. Second, perfusion with 4% paraformaldehyde was performed to fix cerebral tissues.

Quantitative analysis of gene expression was performed using reverse transcription quantitative real-time polymerase chain reaction (hereinafter qRT-PCR). Total

Table 1. Primer pairs for qRT-PCR
Таблица 1. Пары праймеров для qRT-PCR

Праймер / Primer		Последовательность праймера (5'–3') / Primer sequence (5'–3')
Каспаза-3 / Caspase-3	Forward	5'-CAGCCAACCTCAGAGAGACA-3'
	Reverse	5'-GCAGTAGTCGCCTCTGAAGA-3'
Каспаза-1 / Caspase-1	Forward	5'-CTGGGACCCTCAAGTTTGC-3'
	Reverse	5'-AGATCCTCCAGCAGCAACTT-3'
В-клеточная лимфома-2 / B-cell lymphoma 2	Forward	5'-CTTCAGGGATGGGGTGAAC-3'
	Reverse	5'-GCTGGGGCCATATAGTTCCA-3'
Bcl-2-ассоциированный X белок / Bcl-2-associated X protein	Forward	5'-GAGACACCTGAGCTGACCTT-3'
	Reverse	5'-CCCCAGTTGAAGTTGCCATC-3'
Глицеральдегид-3-фосфатдегидрогеназа / Glyceraldehyde-3-phosphate dehydrogenase	Forward	5'-AAGAAGGTGGTGAAGCAGGC-3'
	Reverse	5'-TCCACCACCCTGTTGCTGTA-3'

RNA was isolated from hippocampal tissue samples of BALB/c mice using TRIzol® reagent (Invitrogen, USA) according to the manufacturer's protocol. cDNA was synthesized using a high-efficiency reverse transcription kit for qRT-PCR (ReverTra Ace® qPCR RT Kit, Toyobo, Japan).

Real-time PCR amplification was carried out on an ABI 7500 Fast Real-Time PCR System (Applied Biosystems, USA) using SYBR® Green Realtime PCR Master Mix (Toyobo, Japan). The amplification protocol consisted of initial denaturation at 95 °C for 5 minutes, followed by 40 amplification cycles of 95 °C for 15 s, 65 °C for 30 s, and 72 °C for 30 s, with subsequent melt curve analysis.

Quantitative analysis was performed using threshold cycle (Ct) values determined by the system with automatic baseline setting. Relative gene expression was calculated using the comparative $2^{-\Delta\Delta C_t}$ method, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as a reference gene. Primer sequences are listed in Table 1.

Statistical analysis was conducted using GraphPad Prism version 6.0e for Macintosh (GraphPad Software, USA). Intergroup differences were assessed using two-way analysis of variance (two-way ANOVA) followed by multiple comparisons. The following pairwise comparisons were made: the control group versus the model group, and the GM1 10 mg/kg and GM1 30 mg/kg groups versus the model group. Results are presented as $M \pm SEM$, where M represents the mean and SEM represents the standard error of the mean. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

To assess the effects of ethanol exposure and the potential protective effect of ganglioside GM1 on the expression of genes associated with apoptosis and inflammation in the hippocampus of BALB/c mice, qRT-PCR analysis was performed ($n=10$ per group). A trend toward an increase in caspase-1 mRNA expression was observed in all groups receiving intra-

gastric ethanol (the model, GM1 10 mg/kg, and GM1 30 mg/kg groups) compared with the control group; however, these differences did not reach statistical significance ($p > 0.05$) (Fig. 1a, Table 2). Caspase-3 expression was significantly increased ($p < 0.05$) only in the GM1 30 mg/kg group compared with the model group, with no significant changes observed in the other experimental groups (Fig. 1b, Table 2). Pro-apoptotic BAX expression remained relatively unchanged across all GM1-treated groups, and no statistically significant intergroup differences were observed (Fig. 1c, Table 2). An anomalous change in the expression of the anti-apoptotic gene Bcl-2 was noted: its level in the intact control group differed significantly from that in all other groups exposed to ethanol and the administered GM1 doses (Fig. 1c, Table 2).

Analysis of key gene expression in the mouse hippocampus did not yield a clear picture of the molecular and biochemical processes triggered by ethanol administration and ganglioside GM1 treatment. The most contradictory finding was the statistically significant increase in caspase-3 mRNA levels specifically in the GM1 30 mg/kg group compared with the model group. Caspase-3 is a central effector enzyme that initiates apoptosis. These findings suggest that administration of a high dose of ganglioside GM1 in the setting of chronic alcohol intoxication does not suppress but rather may potentiate apoptotic signals in hippocampal neurons. This unexpected effect requires further investigation, as it contradicts the proposed neuroprotective role of gangliosides.

At the same time, the absence of significant changes in pro-apoptotic BAX expression across all groups, together with the anomalous Bcl-2 expression in the control group, underscores the complexity and nonlinearity of apoptotic pathway regulation in this experimental model. The anomaly in the control group may reflect stress from procedures unrelated to ethanol administration, emphasizing the importance of rigorous control group management.

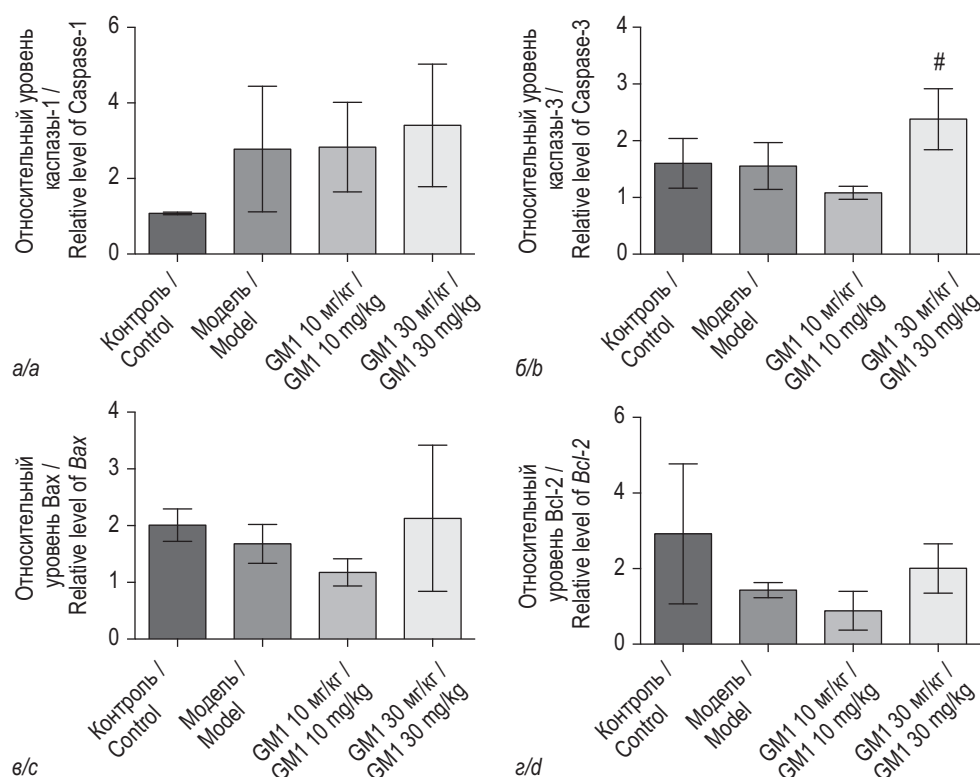


Fig. 1. Evaluation of the activation of apoptotic genes in the hippocampus following intraperitoneal administration of exogenous ganglioside GM1 at different concentrations in a model of long-term ethanol intoxication: *a* — the relative level of caspase-1 was increased in the Model, GM1 10 mg/kg, and GM1 30 mg/kg groups; *b* — the relative expression level of caspase-3 was statistically significantly increased in the GM1 30 mg/kg group; *b* — the relative expression level of BAX was not statistically significant; *c* — the relative expression level of Bcl-2 was not statistically significant. # $p=0.0208$ (Model vs. GM1 30 mg/kg)

Рис. 1. Оценка активации апоптотических генов в гиппокампе при внутрибрюшном введении экзогенного ганглиозида GM1 в разных концентрациях на модели длительной интоксикации этанолом: *a* — относительный уровень каспазы-1 повышен в граппах «модель», GM1 10 мг/кг и GM1 30 мг/кг; *б* — относительный уровень экспрессии каспазы-3 был статистически значимо повышен в группе GM1 30 мг/кг; *в* — относительный уровень экспрессии BAX не показал статистически значимых данных; *г* — относительный уровень экспрессии Bcl-2 не показал статистически значимых данных. # $p=0,0208$ («модель» против GM1 30 мг/кг)

Table 2. Intergroup differences in the results of apoptotic gene expression in the qRT-PCR test

Таблица 2. Межгрупповые различия результатов экспрессии апоптотических генов в тесте qRT-PCR

Группы / Groups	M	95% ДИ / 95% CI	p
Каспаза-1 / Caspase-1			
Контроль / Control vs. Модель / Model	-1,703	От -4,271 до 0,8644 From -4,271 to 0,8644	0,2677
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	-0,05339	От -2,371 до 2,264 From -2,371 to 2,264	0,9999
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	-0,6259	От -3,047 до 1,795 From -3,047 to 1,795	0,8796
Каспаза-3 / Caspase-3			
Контроль / Control vs. Модель / Model	0,04697	От -0,7098 до 0,8038 From -0,7098 to 0,8038	0,9979
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,4732	От -0,2100 до 1,156 From -0,2100 to 1,156	0,2355
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	-0,8247	От -1,538 до -0,1112 From -1,538 to -0,1112	0,0208 [#]
Bcl-2			
Контроль / Control vs. Модель / Model	1,489	От -0,5065 до 3,484 From -0,5065 to 3,484	0,1742
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,5465	От -1,206 до 2,299 From -1,206 to 2,299	0,7919
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	-0,5757	От -2,423 до 1,272 From -2,423 to 1,272	0,7922

Окончание табл. 2 / Ending of the Table 2

Группы / Groups	M	95% ДИ / 95% CI	p
BAX			
Контроль / Control vs. Модель / Model	0,3300	От -0,9970 до 1,657 / From -0.9970 to 1.657	0,8911
Модель / Model vs. GM1 10 мг/кг / GM1 10 mg/kg	0,5025	От -0,6953 до 1,700 / From -0.6953 to 1.700	0,6354
Модель / Model vs. GM1 30 мг/кг / GM1 30 mg/kg	-0,4514	От -1,702 до 0,7997 / From -1.702 to 0.7997	0,7335

Note: CI — confidence interval; M — mean difference.

Примечание: ДИ — доверительный интервал; М — среднее арифметическое.

With regard to inflammatory markers, the modest increase in caspase-1 mRNA levels observed in all ethanol-treated groups is consistent with evidence that alcohol intoxication can activate the inflammasome and proinflammatory cascades. Nevertheless, the lack of statistical significance suggests that either the effect is modest or a larger sample size is required to detect it. Overall, these findings reveal a complex and somewhat paradoxical effect of ethanol and GM1 on the expression of genes governing apoptosis and inflammation in the hippocampus. The key finding is the absence of a clear neuroprotective effect of GM1 at the transcriptional level in this model, along with a potential pro-apoptotic effect of the high GM1 dose, which warrants further investigation to elucidate the underlying mechanisms. Additional experiments, including assessment of not only mRNA levels but also active forms of the proteins studied, as well as histological analysis, are needed to clarify the overall picture.

CONCLUSIONS

1. When evaluating the effect of ganglioside GM1 on the transcriptional activity of key apoptosis-related genes in the mouse hippocampus under conditions of ethanol-induced neurotoxicity, the expected suppressive effect on the expression of the studied markers was not observed. mRNA levels of the pro-apoptotic gene BAX and the anti-apoptotic gene Bcl-2 did not undergo significant changes. Similarly, caspase-1 gene expression showed only a statistically non-significant trend toward an increase.

2. The key finding was the identification of a potential pro-apoptotic effect of the high dose of ganglioside GM1 (30 mg/kg), which was manifested as a statistically significant increase in mRNA levels of caspase-3, a central effector of apoptosis.

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ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Variants of pathological changes of feet in children with Klippel–Trenaunay syndrome

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ABSTRACT

Background. The severity of foot deformities in embryonic type dysplasia of the great veins of the lower extremities (Klippel–Trenaunay syndrome) varies depending on the severity of vascular damage. Hypertrophy of the limbs or individual segments can range from insignificant to extremely pronounced. Klippel–Trenaunay syndrome is often combined with orthopedic pathologies such as macro- and microdactyly, syndactyly, flat feet, and contractures.

Aim — to analyze the variants of pathological changes in the feet in children with Klippel–Trenaunay syndrome of varying severity.

Materials and methods. The work is based on the results of examining 73 patients with embryonic type dysplasia of the great veins (ETMGV) aged from 0 to 18 years, who were treated from 2014 to 2024. According to the severity of the pathology, four groups of patients were identified — with mild, moderate, severe and extremely severe degrees of ETMGV (Klippel–Trenaunay syndrome includes only moderate, severe and extremely severe degrees of ETMGV).

Data processing was performed using the STATISTICA 6.0 and Excel2007 computer programs.

Results. Patterns of increase in the length and circumference of the feet in patients with Klippel–Trenaunay syndrome were determined. Statistical analysis of the average difference in foot lengths and the asymmetry coefficient was performed in groups of patients compiled in accordance with the severity of the syndrome. An increase in the severity of foot length asymmetry was found with an increase in the severity of Klippel–Trenaunay syndrome. As a result of examination of 73 children, equinus contracture of the feet of the affected limb was detected by us in 5 patients (6.84%), of which 2 (2.7%) had a severe degree, and 3 (4.1%) had an extremely severe degree. Split foot was detected in one patient (1.4%) with a severe degree. "Spherical" foot shape was detected in 3 children (4.1%) with an extremely severe degree of the syndrome.

Conclusions. Changes in the length and circumference of the foot of the affected lower limb in patients with Klippel–Trenaunay syndrome are directly dependent on the severity of the syndrome. Correlations were determined between the severity of the syndrome and an increase in the size of the limbs (calf circumference, thigh length and overall limb length, foot length and circumference, calf length and thigh circumference). Variants of changes in the feet were identified according to the degree of expression of cosmetic changes and changes that impair their function.

Keywords: gigantism, Klippel–Trenaunay syndrome, multiple angiokeratomas, port wine spots, foot deformities

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Варианты патологических изменений стоп у детей с синдромом Клиппеля–Треноне различной степени тяжести

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РЕЗЮМЕ

Актуальность. Выраженность деформаций стоп при дисплазии магистральных вен нижних конечностей эмбрионального типа (синдром Клиппеля–Треноне) варьирует в зависимости от степени тяжести поражения сосудов. Гипертрофия конечностей или отдельных сегментов колеблется от незначительной до чрезвычайно выраженной. Синдром Клиппеля–Треноне нередко сочетается с ортопедической патологией: макро- и микродактилией, синдактилией, плоскостопием и различными контрактурами.

Цель — проанализировать варианты патологических изменений стоп у детей с синдромом Клиппеля–Треноне различной степени тяжести.

Материалы и методы. В работе использованы результаты обследования 73 пациентов с эмбриональным типом дисплазии магистральных вен (ДМВЭТ) в возрасте от 0 до 18 лет, находившихся на лечении в хирургической клинике СПбГПМУ с 2014 по 2024 год. Выделены четыре группы пациентов по степени тяжести — легкая, средняя, тяжелая и крайне тяжелая степень ДМВЭТ (синдром Клиппеля–Треноне включает только среднюю, тяжелую и крайне тяжелую степени ДМВЭТ).

Данные обрабатывали с помощью компьютерных программ STATISTICA 6.0 и Excel 2007.

Результаты. Определены закономерности увеличения длины и окружности стоп у пациентов с синдромом Клиппеля–Треноне. Статистический анализ средней разницы длин стоп и коэффициента асимметрии проводился в группах пациентов, составленных в соответствии со степенью тяжести синдрома. Выявлено увеличение выраженности асимметрии длин стоп при нарастании степени тяжести синдрома Клиппеля–Треноне. В результате обследования 73 детей эквинусная контрактура стоп пораженной конечности отмечалась у 5 (6,84%) пациентов, из них при тяжелой степени — у 2 (2,7%), и при крайне тяжелой степени у 3 (4,1%) детей. Расщепленная стопа выявлена у одного пациента (1,4%) с тяжелой степенью. «Шарообразная» форма стопы — у 3 (4,1%) детей с крайне тяжелой степенью синдрома.

Выводы. Отмечается прямая зависимость изменения длины и окружности стопы пораженной нижней конечности у пациентов с синдромом Клиппеля–Треноне от степени тяжести синдрома. Определены корреляции увеличения размера конечностей со степенями тяжести синдрома. Выделены варианты изменений стоп по степени выраженности косметических изменений и изменений, нарушающих их функцию.

Ключевые слова: гигантизм, синдром Клиппеля–Треноне, множественные ангиокератомы, «портвейные» пятна, деформации стоп

Как цитировать

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BACKGROUND

In 1900, the French neuropathologists M. Klippel and R. Trenaunay first described the characteristic symptoms that constitute the triad of this syndrome [1]. Based on numerous studies published in the 20th century on different types of limb enlargement, in 1921, Gassel conducted a review of 53 patients with hemihypertrophy [2].

The prevalence of Klippel–Trenaunay syndrome ranges from one to five cases per 100,000 people, and sex does not influence the likelihood of its development [3]. Limb growth is proportional to the general growth of the child, and vascular anomalies persist throughout life [4]. These processes may be accompanied by anomalies of the soft tissues, bones and changes in limbs length [5, 6]. The main sign of the syndrome is a triad of symptoms: vascular stains, abnormal varicose veins, and hypertrophy of the soft tissues and bone structures, with an increase in the length and volume of the limb. This syndrome is a manifestation of embryonic-type main vein dysplasia (ETMVD) [7]. According to the classification by D. Kupatadze, ETMVD can be presented in mild, moderate, severe and extremely severe forms [7]. The mild form of ETMVD does not include all signs of Klippel–Trenaunay syndrome, since there is no increase in the volume and length of the limb, therefore, the syndrome includes ETMVD of moderate, severe, and extremely severe degrees.

The severity of deformities in the syndrome varies depending on the severity of the vascular lesions: the more serious the vascular involvement, the more pronounced the deformities. Hypertrophy of individual limb segments can be either minor or very pronounced. Since bone tissue is not involved in the pathological process, only an increase in the limb circumference is observed. Klippel–Trenaunay syndrome is often accompanied by orthopedic pathology, such as macro- and microdactyly, syndactyly, and flatfoot [8].

According to literature sources [6, 9, 10, 11], the lower limbs are affected most often: an increase in the volume and length of the foot is noted, and less often, lengthening of the entire limb. These changes may lead to secondary deformities of the spine, pelvis, adjacent joints, and symmetrical limbs, which disrupts biomechanics and functions. It is clear that, in the absence of timely correction, a number of orthopedic complications may occur.

Despite a large number of studies on the treatment of vascular malformations, orthopedic disorders are considered concomitant pathologies that receive insufficient attention, especially regarding the possibility of their orthopedic correction. Issues related to pathological changes of the feet and the planning of the scope and stages of surgical orthopedic therapy remain insufficiently covered.

Hypertrophy of the lower limbs occurs in 95% of cases [12–15] and manifests as an increase in their length

and/or circumference [13]. In the literature, descriptions of foot deformities and enlargement are general in nature, without detailed specification [16–18]. In patients with moderate Klippel–Trenaunay syndrome, changes in foot configuration are observed, accompanied by moderately pronounced cosmetic imperfections. Consequently, there were no indications for surgical orthopedic correction.

Changes in foot configuration in children with severe Klippel–Trenaunay syndrome

Changes in foot configuration in children with severe degree of the disease were divided by us into two levels according to objective cosmetic criteria.

- *Moderately pronounced* changes were defined as those that do not create a significant cosmetic defect and do not interfere with the choice and use of footwear.
- *Pronounced changes* were defined as foot configurations that cause a significant cosmetic defect and reduce the child's quality of life.

In case of significant foot enlargement associated with uneven load distribution on the lower limbs and impaired weight-bearing function of the affected limb, the gait pattern changes. Over time, these changes may cause scoliotic deformation and early development of arthrosis in the lower limbs.

The most pronounced changes in foot configuration were observed in children with extremely severe Klippel–Trenaunay syndrome. In the region of the dorsal and plantar surfaces of the feet, an excess volume of soft tissues, including subcutaneous fat and vascular malformations, was observed. The soft tissues were distributed unevenly, giving the foot a spherical shape. In three patients with an extremely severe degree of the syndrome, a spherical shape of the foot on the affected limb was observed. Dysplastic changes involved all soft tissues of the foot, lower leg, and thigh. As a result, these patients experienced constant pain syndrome, and in an upright position they could remain for no more than three minutes without the use of compression hosiery (Table 1).

MATERIALS AND METHODS

This study is based on data obtained from the examination and treatment of 73 patients with embryonic-type main vein dysplasia (ETMVD) aged 0–18 years, who were treated between 2014 and 2024 in the surgical departments of Pediatric University.

The severity of embryonic-type main vein dysplasia was determined according to the classification of D.D. Kupatadze. It should be noted that this classification is aimed at systematizing vascular changes in this pathology and is widely used by pediatric vascular surgeons for planning the correction of the vascular component. However, pathological changes in the

Table 1. The frequency of cosmetic defects of the feet and the frequency of violations of the “support” of the feet, depending on the severity of vascular pathology**Таблица 1.** Частота косметических дефектов стоп и частота нарушения «опорности» стоп в зависимости от степени тяжести сосудистой патологии

Степень тяжести дисплазии магистральных вен эмбрионального типа / Degree of severity embryonic type dysplasia of the great veins		Патологические изменения стоп / Pathological changes in the feet			
		частота косметических дефектов / frequency of cosmetic defects		нарушения «опорности» стопы / violations of the “support” of the foot	
		умеренно выраженные / moderate symptoms	выраженные / expressed	средней степени / medium degree	тяжелой степени / severe degree
Легкая / Light		0	0	0	0
Синдром Клиппеля–Треноне / Klippel–Trenaune syndrome	Средней тяжести / Moderate severity	9 (12,3%)	0	3 (4,1%)	0
	Тяжелая / Severe degree	5 (6,2%)	17 (23,3%)	21 (28,8%)	5 (6,2%)
	Крайне тяжелая / Extremely severe degree	0	7 (9,6%)	0	7 (9,6%)

Table 2. Severity of pathology in children with embryonic type of great vein dysplasia, depending on gender and clinical picture of Klippel–Trenaunay syndrome**Таблица 2.** Степени тяжести поражения у детей с эмбриональным типом дисплазии магистральных вен, в зависимости от пола и клинической картины синдрома Клиппеля–Треноне

Степень поражения / Degree of damage		Клиническая картина / Clinical picture		Пол / Gender	
Легкая / Light		1. «Гладкие» сосудистые пятна. / “Smooth” vascular spots. 2. Атипичные, эмбриональные вены (в пределах сегментов конечности). / Atypical, embryonic veins (within the segments of the limb).		м	ж
Клиническая картина синдрома Клиппеля–Треноне / Klippel–Trenaunay Syndrome clinical picture	Средняя, 3, 4, 5, 6 — дополнительно к предыдущим симптомам / Average 3, 4, 5, 6 — in addition to the previous symptoms	3. Симметричное увеличение окружности конечности / Symmetrical increase in limb circumference. 4. Несимметричная гипертрофия. / Asymmetrical hypertrophy. 5. Бугристые сосудистые пятна. / Tuberous vascular spots. 6. Местный синдром диссеминированного внутрисосудистого свертывания. / Local disseminated vascular coagulation syndrome. Соответствует клинической картине синдрома Клиппеля–Треноне / Corresponds to the clinical picture of Klippel–Trenaunay syndrome		7	4
	Тяжелая, 7, 8, 9, 10, 11, 12, 13, 14 — дополнительно к предыдущим симптомам / Severe 7, 8, 9, 10, 11, 12, 13, 14 — in addition to the previous symptoms	7. Гигантизм стоп, макродактилия. / Foot gigantism, macrodactyly. 8. «Элефантиаз». / “Elephantiasis”. 9. Контрактуры. / Contractures. 10. Нарушения функции конечности. / Limb function disorders. 11. Поражение тканей двух конечностей и более. / Damage to the tissues of two or more limbs. 12. Эмбриональные вены распространяются на всю конечность. / Embryonic veins spread to the entire limb. 13. Поражение сосудов органов малого таза. / Damage to the vessels of the pelvic organs. 14. Распространенный синдром диссеминированного внутрисосудистого свертывания. / A common disseminated vascular coagulation syndrome. Соответствует клинической картине синдрома Клиппеля–Треноне / Corresponds to the clinical picture of Klippel–Trenaunay syndrome		16	14
	Крайне тяжелая, 15, 16, 17, 18, 19 — дополнительно к предыдущим симптомам / Extremely severe 15, 16, 17, 18, 19 — in addition to the previous symptoms	15. Уродующая гипертрофия конечности. / Disfiguring limb hypertrophy. 16. «Венозные соты» на голени. / “Venous honeycombs” on the lower leg. 17. Головокружение, коллаптоидные состояния, потеря сознания после кратковременной ходьбы без эластичных бинтов. / Dizziness, collaptoic states, loss of consciousness after short-term walking without elastic bandages. 18. Мелена и гематурия. / Melena and hematuria. 19. Кисты и лимфангиомы брюшной: полости и забрюшинного пространства. / Cysts and lymphangiomas of the abdominal cavity and retroperitoneal space. Соответствует клинической картине синдрома Клиппеля–Треноне / Corresponds to the clinical picture of Klippel–Trenaunay syndrome		5	2

limbs are described schematically in this classification and are not fully characterized, which limits its use for assessing orthopedic disorders.

Thus, in our study, a detailed analysis of foot pathology was performed in patients with each degree of disease severity to develop prospective plans for the scope and stages of surgical orthopedic correction.

Of 73 patients, 11 children had mild ETMVD (10.9 ± 1.7 years), 25 children had moderate ETMVD (13.0 ± 0.65 years), 30 children had severe ETMVD (10.2 ± 0.7 years) and 7 children had extremely severe ETMVD (8.9 ± 2.4 years).

In Table 2, the patients are distributed according to the D.D. Kupatadze classification depending on the severity of EMTVD and sex. The severity levels of EMTVD corresponding to the clinical presentation of Klippel–Trenaunay syndrome are also highlighted.

The circumference of the forefoot was measured using a tape at the level of the metatarsophalangeal joints. Foot length was assessed using the Fridland method: the foot was placed on a clean sheet of paper, and its contours were outlined with a pencil in a vertical position. Then, the foot length was measured along the contour from the tip of the toes to the posterior end of the heel using a ruler or measuring tape.

When analyzing the results, not only the difference between the healthy and affected foot was considered, but the asymmetry coefficient (AC) was also calculated:

$$AC = (L2 - L1) \cdot 100 / L1,$$

where L1 is the length of the affected foot (the larger measurement); L2 is the length of the normal foot (the smaller measurement). In addition to length measurement, the contourgram made it possible to determine the enlargement of individual rays and to draw conclusions about the form of foot involvement. The height of the longitudinal arch of the foot, defined as the vertical distance from the floor to the highest point of the plantar surface (area of the navicular bone), was used to assess the condition of the arch. Then, the Friedland podometric index (FPI) was calculated:

$$FPI = (\text{foot height} \cdot 100) / \text{foot length}.$$

FPI interpretation:

- more than 31 — high arch;
- from 31 to 29 — normal arch;
- from 29 to 27 — lowered arch;
- from 27 to 25 — flatfoot;
- less than 25 — pronounced flatfoot.

These measurements were obtained in adolescents with completed foot growth and without pronounced excess soft tissue in the plantar area. In preschool- and primary school-age children, normative data for arch height do not exist. All measurements were performed

in the standing position with weight. The determination of hindfoot pronation (heel pronation) was carried out as follows: an axis was drawn along the posterior surface of the leg through the midline of the Achilles tendon to the middle of the calcaneal tuberosity. Deviation of the axis outward from the vertical line indicated the angle of pronation of the hindfoot, i.e., the heel. Under normal conditions, the heel axis coincides with the plumb line drawn through the middle of the Achilles tendon.

Instrumental methods of orthopedic examination

To diagnose foot pathology, different instrumental methods were used. Radiography was performed using Philips CombiDiagnost R90 (Germany). By allowing the assessment of the bone structures of the foot of the affected limb, radiography helped to identify the presence of true hypertrophy. The study was conducted on symmetrical areas of the both limbs in order to perform a comparative analysis.

The vessels were examined using a GE Innova 3100 (USA). Phlebography was necessary for a comprehensive examination of the main veins in children. Fig. 1 shows the pathological venous bed of the limb.

Ultrasound examination of the vessels and soft tissues was performed using a Philips Affiniti 50 apparatus (Netherlands). An ultrasound image of the pathological changes in the vein bed is presented in Fig. 2.

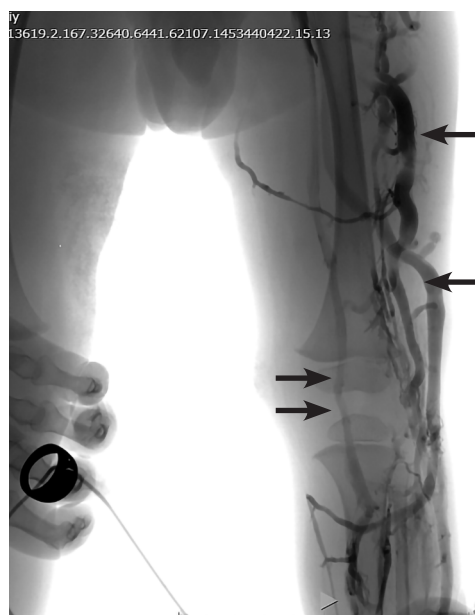


Fig. 1. Phlebography of the left lower limb of patient Ch., 1 year 8 months; Diagnosis: embryonic type dysplasia of the great veins of the left lower extremity. The lateral embryonic vein is indicated by single arrows; the hypoplasia of the popliteal segment of the deep femoral vein is indicated by a double arrow

Рис. 1. Флебография левой нижней конечности пациента Ч., 1 год 8 месяцев. Диагноз: дисплазия магистральных вен эмбрионального типа левой нижней конечности. Латеральная эмбриональная вена обозначена одинарными стрелками; гипоплазия подколенного сегмента глубокой бедренной вены обозначена двойной стрелкой

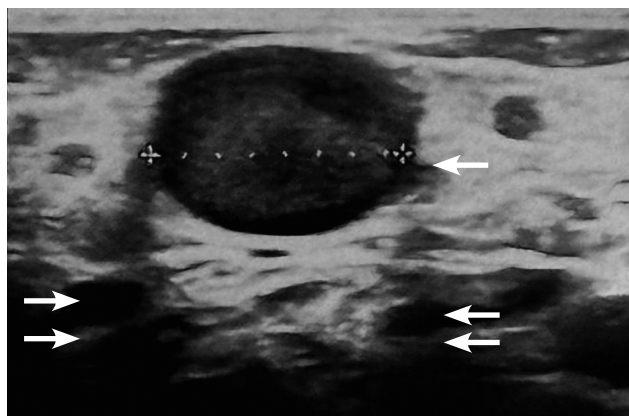


Fig. 2. Ultrasound of the veins of the upper third of the lower leg, patient Ch., 10 years old. Diagnosis: embryonic type dysplasia of the great veins of the left lower extremity. The lateral embryonic vein is indicated by a single arrow; the dilated tributaries of the embryonic vein are indicated by double arrows

Рис. 2. Ультразвуковое исследование вен верхней трети голени, пациент Ч., 10 лет. Дисплазия магистральных вен левой нижней конечности эмбрионального типа. Латеральная эмбриональная вена обозначена одинарной стрелкой; дилатированные притоки эмбриональной вены обозначены двойными стрелками

Klippel–Trenaunay syndrome may be diagnosed after birth according to phenotypic signs. To confirm the diagnosis, patients underwent ultrasound examination of the lower limb vessels and venography. The main pathological changes in the surface veins were determined during ultrasound examination, including an excessively pronounced and tortuous venous network with varicose changes and the presence of embryonic lateral veins. In the deep veins, hypoplasia of the popliteal segment of the femoral vein of varying severity was found; similar data are reported in the literature [11].

Phlebography of the affected limb was performed in all patients. The main aim of this examination was to confirm the diagnosis. Additionally, the deep veins were assessed in order to plan potential surgical operations involving the superficial veins, the lateral embryonic vein and the deep veins. The literature also reports the use of these methods for clarification and preoperative planning [12–14].

Statistical analysis

The normality of the distribution of variables was assessed using kurtosis and skewness indices, which characterize the shape of the Gaussian distribution curve. Parametric statistical methods, including the calculation of Student's t-test, were used to process the results, as the distribution of values in the samples was close to normal.

For variables with a continuous distribution, the arithmetic mean (M) and the standard error of the mean (m) were calculated, whereas for variables with discrete values, the frequency of occurrence was determined.

For correlation analysis, Pearson correlation coefficient was used, taking into account its absolute value

and the level of statistical significance, which depends on the sample size and allows the assessment of sufficiently strong correlations.

Data processing was performed using STATISTICA 6.0 and Microsoft Excel 2007.

RESULTS AND DISCUSSION

During the study, pathological changes in the feet of children with various degrees of EMTVD were analyzed: mild, moderate, severe, and extremely severe.

Foot changes in mild embryonic-type main vein dysplasia

Eleven children with mild EMTVD were examined. In 6 adolescents (13 years old – 1 individual, 14 years



Fig. 3. Patient A., 8 years old, diagnosis: in embryonic type dysplasia of the great veins of the lower extremities moderate severity. Increase in length and circumference of toes III, IV, and V

Рис. 3. Пациент А., 8 лет, с диагнозом: дисплазия магистральных вен эмбрионального типа средней степени тяжести. Увеличение длины и окружности III, IV и V пальцев стопы



Fig. 4. Patient B., 4 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities moderate severity. In patients with moderate severity, an increase in the forefoot was recorded with an increase in the circumference and length of the fingers

Рис. 4. Пациент Б., 4 года. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа, средней степени тяжести. У пациента со средней степенью тяжести зафиксировано увеличение переднего отдела стопы, окружности и длины пальцев

old – 2 individuals, 15 years old – 2 individuals, and 16 years old – 1 person), a decrease in the height of the longitudinal arch of the foot was revealed. In the remaining five cases, no foot pathology was observed.

Foot changes in moderate embryonic-type main vein dysplasia (Klippel–Trenaunay syndrome)

Twenty-five children with moderate Klippel–Trenaunay syndrome were examined. Among them:

- in 12 adolescents, a decrease in the height of the longitudinal arch of the foot was revealed;
- in 4 patients, a valgus foot position was found;
- in 5 patients, an increase in the length and circumference of one or more toes was noted (Fig. 3);
- in 3 patients, an enlargement of the forefoot with an increase in the circumference and length of the toes was recorded (Fig. 4);
- in one child, pachydermodactyly was registered — an increase in skin thickness without a significant change in the thickness of the subcutaneous fat.

Foot changes in severe embryonic-type main vein dysplasia (Klippel–Trenaunay syndrome)

Thirty patients with severe Klippel–Trenaunay syndrome (severe ETMVD) were examined.

In children with severe Klippel–Trenaunay syndrome, pathological changes in the feet were more pronounced:

- a decrease in the height of the longitudinal arch of the affected foot was found in 4 adolescents;
- a valgus foot position was detected in 2 patients;
- in 7 children, an enlargement of the forefoot combined with a uniform increase in the toe circumference was observed (see Fig. 3);
- in 5 patients, an enlargement of individual rays of the foot was recorded (Fig. 5);



Fig. 5. Patient A., 5 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities severe severity. Enlargement of rays I and II of the right foot

Рис. 5. Пациент Г., 5 лет. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа тяжелой степени. Увеличение I и II лучей правой стопы



Fig. 6. Patient G., 7 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities severe severity. Splitting the left foot

Рис. 6. Пациент Г., 7 лет. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа тяжелой степени. Вариант расщепления левой стопы



Fig. 7. Patient N., 11 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities severe severity. Increase in the circumference of all parts of the right foot, with a slight increase in length and circumference of the fingers

Рис. 7. Пациент Н., 11 лет. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа тяжелой степени. Увеличение окружности всех отделов правой стопы с незначительным увеличением длины и увеличением окружности пальцев



Fig. 8. Patient K., 13 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities severe severity. Equinus contracture of the left foot

Рис. 8. Пациент К., 13 лет. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа тяжелой степени. Эквиносная контрактура левой стопы

- in 4 patients, an increase in the toe circumference was noted, mainly due to vascular malformations of the soft tissues;
- in 2 children, an enlargement of individual rays of the foot combined with clinodactyly was revealed;
- in one patient, a deformity resembling a split-foot type was found (Fig. 6);
- in 3 patients, an increase in the circumference of all parts of the foot with a slight increase in length, as well as an increase in the circumference of all or several toes, was noted (Fig. 7);
- equinus contracture of the affected foot was detected in 2 children (Fig. 8).

Foot changes in extremely severe embryonic-type main vein dysplasia (Klippel–Trenaunay syndrome)

Seven patients with extremely severe Klippel–Trenaunay syndrome (extremely severe EMTVD) were examined. In this group, foot pathology was most pronounced:

- in the region of the dorsal and plantar surfaces of the feet, an excessive volume of soft tissue was observed, including subcutaneous fat and vascular malformations; the soft tissues of the foot were distributed unevenly;
- uneven enlargement of all parts of the foot combined with total syndactyly of the II, III, and IV toes was found in 1 patient (Fig. 9);
- a «spherical» shape of the foot of the affected limb was noted in 3 patients (Fig. 10);
- equinus contracture of the foot was detected in 3 patients, and the contracture was rigid in nature.

The frequency of identified foot changes in patients with EMTVD is presented in Table 3.



Fig. 9. Patient S., 3 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities extremely severe severity. Uneven enlargement of all parts of the right foot with a total form

Рис. 9. Пациент С., 3 года. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа крайне тяжелой степени. Неравномерное увеличение всех отделов правой стопы с тотальной формой

It was found that the circumference of the lower leg, thigh length and total limb length showed statistically significant positive correlations with the severity of Klippel–Trenaunay syndrome ($p \leq 0.001$). Also, lower leg length, thigh circumference, foot length and circumference were positively correlated with disease severity ($p \leq 0.01$). No statistically significant association was found between patient age and the severity of the syndrome ($r=0.13$, $p > 0.05$).

CONCLUSION

1. Thirteen types of pathological foot changes were identified;

2. Indications for surgical treatment were established in children with severe (21) and extremely severe (7) Klippel–Trenaunay syndrome.

3. Lower leg length, thigh circumference, and foot length and circumference showed significant positive correlations with disease severity ($p \leq 0.01$).

4. No statistically significant association was found between syndrome severity and patient age ($r = 0.13$, $p > 0.05$).

5. The differentiation of pathological changes depending on the severity of cosmetic and functional changes in the feet contributes to optimizing the choice of orthopedic surgical correction in the future.

Our study revealed a diversity of pathological changes in the feet of children with different severity levels of Klippel–Trenaunay syndrome. Statistically significant correlations were found between foot length and circumference, as well as between lower leg length, thigh circumference, lower leg circumference, thigh length, total limb length, and syndrome severity.

Based on the obtained results, a classification of pathological changes according to the severity of cosmetic and functional foot disorders has been proposed. This approach may serve as a guide for determining the indications and surgical strategy for future orthopedic correction.



Fig. 10. Patient S., 15 years old. Diagnosis: in embryonic type dysplasia of the great veins of the lower extremities extremely severe severity. «Ball-shaped» form of the right foot

Рис. 10. Пациент Т., 15 лет. Диагноз: дисплазия магистральных вен нижней конечности эмбрионального типа крайне тяжелой степени. «Шарообразная» форма правой стопы

Table 3. Frequency of pathological changes in the feet of children with dysplasia of the great veins of the lower extremities of varying severity lippeI–Trenone syndrome**Таблица 3.** Частота патологических изменений стоп у детей с дисплазией магистральных вен нижней конечности эмбрионального типа различной степени тяжести Синдром Клиппеля–Треноне

Характер изменений / The nature of the changes	Степень тяжести дисплазией магистральных вен нижней конечности эмбрионального типа / Severity of embryonic type dysplasia of the main veins of the lower extremity			
	легкая / light	средняя / average	тяжелая / severe	крайне тяжелая / extremely severe
Снижение высоты продольного свода стопы / Lowering the height of the longitudinal arch of the foot	6 (8,2%)	12 (16,4%)	4 (5,4%)	*
Вальгусная установка пораженной стопы / Valgus of the affected foot	0	4 (5,4%)	2 (2,7%)	0
Увеличение длины и окружности одного или нескольких пальцев / Increasing the length and circumference of one or more fingers	0	5 (6,2%)	0	0
Пахидермодактилия / Pachydermodactyly	0	1 (1,4%)	0	0
Увеличение переднего отдела стопы с увеличением окружностей пальцев / Enlargement of the forefoot with an increase in the circumference of the fingers	0	3 (4,1%)	7 (9,6%)	0
Увеличение отдельных лучей / Magnification of individual beams	0	0	5 (6,2%)	0
Увеличение окружности пальцев за счет сосудистых мальформаций / Increased finger circumference due to vascular malformations	0	0	4 (5,4%)	0
Увеличение отдельных лучей в сочетании с клинодактилией / Magnification of individual rays in combination with clinodactyly	0	0	2 (2,7%)	0
Расщепленная стопа / Split foot	0	0	1 (1,4%)	0
Увеличение всех отделов стопы с незначительным увеличением длины и окружности пальцев / Enlargement of all parts of the foot with a slight increase in the length and circumference of the toes	0	0	3 (4,1%)	0
Эквинусная контрактура / Equinus contracture	0	0	2 (2,7%)	3 (4,1%)
Неравномерное увеличение всех отделов стопы с синдактилией нескольких пальцев / Uneven enlargement of all parts of the foot with syndactyly of several fingers	0	0	0	1 (1,4%)
«Шарообразная» форма стопы / The «spherical» shape of the foot	0	0	0	3 (4,1%)

* It was not possible to evaluate the height of the longitudinal arches of the feet in patients with extremely severe vascular pathology due to the excess volume of soft tissue in the plantar surface area.

* Провести оценку высоты продольных сводов стоп у пациентов с крайне тяжелой степенью сосудистой патологии не представлялось возможным в связи с избыточным объемом мягких тканей в области подошвенной поверхности.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Anti-addictive potential of the dual incretin receptor agonist tirzepatide in a model of emotional overeating induced by intracranial self-stimulation

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ABSTRACT

Background. The incretin system (GLP-1 and GIP) plays a key role in the regulation of energy metabolism and feeding behavior. Recent research has demonstrated that incretin receptor agonists can modulate not only metabolic processes but also neuronal mechanisms of reward, highlighting their potential use in managing impulsive and addictive disorders.

Aim — to assess the effect of the dual incretin receptor agonist tirzepatide on operant and feeding behavior in rats in the intracranial self-stimulation (ICSS) test.

Material and methods. The experiment involved 24 male Wistar rats. Tirzepatide was administered subcutaneously (s.c.) at doses of 0.05, 0.10, and 0.30 mg/kg once daily for 7 days. Behavioral testing was performed 1 hour after injection, including the ICSS test (number of lever presses per minute) and the feeding test (number of seeds eaten per minute). Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's post hoc test ($p < 0.05$).

Results. A single administration of tirzepatide produced no significant differences compared with control ($H=3.5$; $p=0.38$). On day 3, a significant reduction in lever-pressing was observed at 0.30 mg/kg (approximately 15–20% below control; $H=13.69$; $p < 0.001$; Dunn $p < 0.01$) along with a decrease in food intake ($H=9.64$; $p < 0.05$; Dunn $p < 0.05$). By day 7, a stable dose-dependent suppression of both operant and feeding behavior was recorded (ICSS: $H=13.13$; $p < 0.01$; feeding: $H=14.16$; $p < 0.01$) with significant differences at 0.10 and 0.30 mg/kg.

Conclusion. Repeated administration of tirzepatide, a dual incretin receptor agonist, produces a pronounced dose- and time-dependent reduction in motivational and feeding activity in rats.

Keywords: incretins, tirzepatide, GLP-1, GIP, brain self-stimulation, reward system, impulsive behavior, addictive behavior

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Антиаддиктивный потенциал двойного агониста инкретиновых рецепторов тирзепатида в тесте на эмоциональное переживание, вызванное внутримозговой самостимуляцией

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РЕЗЮМЕ

Актуальность. Инкретиновая система (GLP-1 и GIP) играет ключевую роль в регуляции энергетического обмена и пищевого поведения. Современные исследования показывают, что агонисты инкретиновых рецепторов способны опосредованно изменять не только метаболические процессы, но и нейрональные механизмы вознаграждения, что открывает перспективы их применения при нарушениях импульсивного и аддиктивного поведения.

Цель исследования — оценить влияние двойного агониста инкретиновых рецепторов тирзепатида на показатели оперантной и пищевой активности у крыс в тесте самостимуляции мозга.

Материалы и методы. В эксперименте использованы 24 самца крыс линии Вистар. Препарат вводили подкожно (s.c.) в дозах 0,05; 0,10 и 0,30 мг/кг один раз в сутки в течение 7 дней. Через 1 час после введения проводили тест внутримозговой самостимуляции (ICSS) и тест пищевого поведения (количество съеденных семян за 1 мин). Для статистического анализа применяли непараметрический критерий Краскела–Уоллиса с последующим пост-хок тестом Данна ($p < 0,05$).

Результаты. После однократного введения тирзепатида различий с контролем не выявлено ($H=3,5$; $p=0,38$). На 3-и сутки наблюдалось достоверное снижение количества нажатий на педаль при дозе 0,30 мг/кг (на ~15–20% ниже контроля; $H=13,69$; $p < 0,001$; Dunn $p < 0,01$) и уменьшение потребления пищи ($H=9,64$; $p < 0,05$; Dunn $p < 0,05$). На 7-е сутки выявлено стойкое дозозависимое снижение как оперантной, так и пищевой активности: ICSS ($H=13,13$; $p < 0,01$) и пищевое поведение ($H=14,16$; $p < 0,01$), достоверные различия при дозах 0,10 и 0,30 мг/кг.

Вывод. Повторное введение двойного агониста инкретиновых рецепторов тирзепатида вызывает выраженное дозо- и время-зависимое снижение мотивационной и пищевой активности у крыс.

Ключевые слова: инкретины, тирзепатид, GLP-1, GIP, самостимуляция мозга, система вознаграждения, импульсивное поведение, аддиктивное поведение

Как цитировать

Деданишвили Н.С., Пюрвеев С.С., Лебедев А.А., Васильев А.Г., Шабанов П.Д., Лебедев Д.А. Антиаддиктивный потенциал двойного агониста инкретиновых рецепторов тирзепатида в тесте на эмоциональное переживание, вызванное внутримозговой самостимуляцией. *Педиатр.* 2025;16(5):44–55. <https://doi.org/10.56871/PED.2025.78.21.005>.

BACKGROUND

Incretins are a group of hormonal peptides of the gastrointestinal tract that are secreted in response to food intake and enhance glucose-dependent insulin secretion by pancreatic β -cells [1]. The main representatives of the incretin system are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), which are synthesized by enteroendocrine L- and K-cells of the small intestine, respectively [2]. After being secreted into the bloodstream, incretins provide fine regulation of energy and carbohydrate metabolism by coordinating the interaction between the gastrointestinal tract, pancreas, central nervous system, and peripheral target organs [3].

Incretins increase insulin release in response to oral glucose administration compared with intravenous administration at the same blood glucose concentration. This effect is observed due to the combined action of GLP-1 and GIP (Fig. 1), which enhances insulin secretion and decreases glucagon production. These effects contribute to the homeostatic control of blood glucose levels [2].

Glucagon-like peptide-1 (GLP-1) is synthesized by proteolytic cleavage of the precursor proglucagon (PPG), which is expressed in enteroendocrine cells of the distal small intestine and the pancreas. Glucose-dependent insulintropic polypeptide (GIP) is encoded by a separate gene and is synthesized in the proximal intestine [2]. Both peptides belong to the glucagon-like peptide family and act through specific G protein-coupled receptors (GPCRs): GLP-1R and GIPR (Fig. 2) [4].

Activation of GLP-1R and GIPR triggers an intracellular cascade that includes increased cAMP levels and activation of protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K). In β -cells, these processes lead to potentiation of insulin secretion [5]. At the same time, glucagon secretion by α -cells is inhibited, and hepatic glucose production is reduced. As a result, postprandial glucose homeostasis is maintained [5]. Additionally, GLP-1 has anorexigenic and gastrointestinal effects: it slows gastric emptying, reduces intestinal motility, and induces a feeling of satiety. These effects underlie the therapeutic use of GLP-1R agonists for weight reduction and the treatment of obesity [6].

Receptors such as GLP-1R and GIPR are expressed in various tissues, reflecting the systemic nature of incretin axis regulation (Fig. 2). Peripheral expression of GLP-1R has been found in the pancreatic islets (on β - and δ -cells), in the heart, kidneys, lungs, liver, adipose tissue, and gastrointestinal tract. GIPRs are predominantly expressed in the pancreas, adipose tissue, bones, and adrenal glands [3].

In addition to peripheral organs, GLP-1R is widely represented in the central nervous system, where it mediates the interaction between metabolic and neurobiological processes. A high density of receptors is observed in the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve, which are key centers for visceral signal integrations, as well as in structures that cross the blood-brain barrier, such as the lateral septum, ventral tegmental area (VTA), nucleus accumbens (NAc),

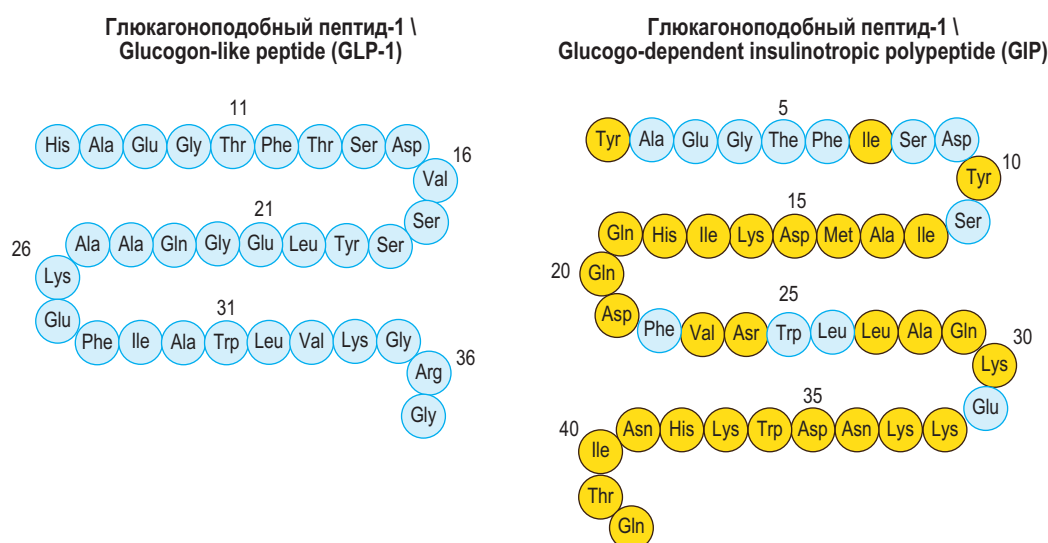


Fig. 1. Structure of incretin peptides: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Amino acid sequences of GLP-1 (left) and GIP (right) are shown, both representing key components of the incretin system that regulates insulin secretion and energy homeostasis

Рис. 1. Структура инкретиновых пептидов: глюкагоноподобного пептида-1 (GLP-1) и глюкозозависимого инсулиотропного полипептида (GIP). Показаны аминокислотные последовательности GLP-1 (слева) и GIP (справа), являющихся основными представителями инкретиновой системы, регулирующей секрецию инсулина и энергетический гомеостаз

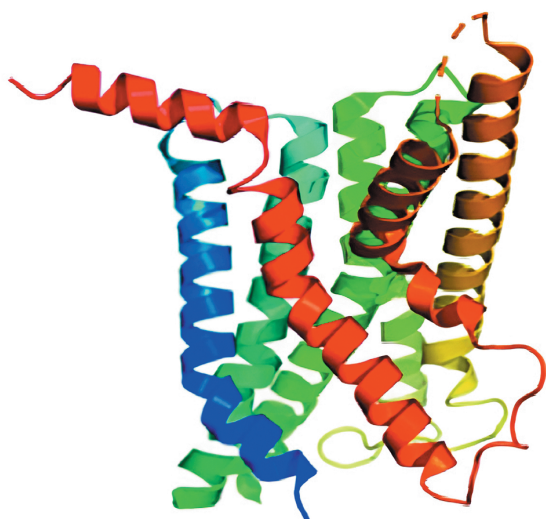


Fig. 2. Three-dimensional structure of the glucagon-like peptide-1 receptor (GLP-1R). Spatial organization of GLP-1R, a G protein-coupled receptor (GPCR) composed of seven transmembrane α -helices that mediate ligand (GLP-1) binding and intracellular signal transduction

Рис. 2. Трехмерная структура рецептора глюкагоноподобного пептида-1 (GLP-1R). Изображена пространственная организация GLP-1R — мембранного рецептора, относящегося к семейству рецепторов, сопряженных с G-белками (GPCR). Рецептор состоит из семи трансмембранных α -спиралей, обеспечивающих связывание лиганда (GLP-1) и передачу сигнала внутрь клетки

hippocampus, amygdala, and bed nucleus of the stria terminalis [4, 7].

Such a distribution of receptors indicates that GLP-1 is involved not only in glycemic control but also in the regulation of appetite, food motivation, reward, cognitive function, and stress responses. Collectively, the effects of incretins provide integration of metabolic, behavioral, and cognitive processes, making the incretin system a unique link between energy metabolism and the central regulation of behavior [8].

The rapid enzymatic degradation of endogenous GLP-1 by dipeptidyl peptidase-IV (DPP-IV) and neutral endopeptidase 24.11 limits its bioavailability, so that only a small fraction of the circulating peptide reaches brain structures [8]. This fact has stimulated the development of degradation-resistant GLP-1 analogues with prolonged action, such as exendin-4, liraglutide, dulaglutide, and semaglutide, which are administered subcutaneously at varying intervals. In clinical practice, DPP-IV inhibitors (sitagliptin, linagliptin) are also used, whereas the GLP-1 receptor antagonist exendin-9-39 is mainly used in experimental studies [9, 10].

In recent years, considerable attention has been paid to the role of the GLP-1 signalling pathway in regulating neurobiological processes beyond metabolism, including the development of addictive behavior. The results of preclinical and clinical studies indicate the involvement of the GLP-1 system in regulating

responses associated with alcohol consumption, allowing it to be considered a potential therapeutic target for disorders related to addictive behavior.

AIM

The aim of the study was to evaluate the effect of the dual incretin receptor agonist tirzepatide on measures of operant and feeding activity in rats using the brain self-stimulation test.

MATERIALS AND METHODS

Animal selection. A total of 24 male Wistar rats (Rappolovo Laboratory Animal Nursery, Leningrad region) were used in the study. Animals were housed in standard plastic cages with 8–10 animals per cage with free access to water and food under inverted light from 8:00 to 20:00 at a temperature of 22 ± 2 °C. All experiments were conducted during the autumn-winter period.

Surgical procedure. When the rats reached a body weight of 250 g, stereotaxic surgery was performed. The rats were anesthetized with Zoletil 100 (tiletamine, zolazepam, Virbac, France) at a dose of 50 mg/kg. Bipolar stainless steel electrodes (0.2 mm in diameter) were implanted under aseptic and antiseptic conditions using a stereotaxic apparatus (Harvard Apparatus, USA). The electrodes were implanted into the right VTA at the following coordinates relative to bregma: AP=−5.3 mm, L=0.8 mm, V=8.2 mm.

Study of self-stimulation response. In a Skinner box (29.2×30.5×24.1 cm), a lever (4.5×2.0 cm) was positioned 3.0 cm above the floor. The chamber was connected to a computer via an interface and controlled by proprietary software (Institute of Experimental Medicine, Russia). Each lever press triggered a train of rectangular pulses lasting 500 ms, with a pulse frequency of 100 Hz and a pulse duration of 1 ms. The animals were trained for 10 min daily over 5 days. During these sessions, the current intensity was adjusted to ensure the maximum rate of lever pressing for each animal without impairing motor function or inducing seizures. Animals that failed to press the lever more than 50 times during the 10-minute sessions were excluded from the experiment. The remaining animals were tested during 30-minute sessions for an additional 5 days to establish a stable baseline response rate [11].

Competition between Self-Stimulation and Eating Behaviour Test. After stabilization of the self-stimulation parameters, a food deprivation regime was introduced. Rats were trained to reach a feeder containing a large number of shelled sunflower seeds for 30 min daily for 5 days in a self-stimulation testing chamber. The self-stimulation lever was deactivated.

Subsequent experiments were conducted under choice conditions between self-stimulation and food consumption: a feeder was placed in the Skinner chamber, and the pedal with a fixed current was activated. All animals were maintained at a stable body weight.

Hypothalamic Stimulation-Induced Behavior

Test. After competition of the self-stimulation and eating behaviour tests, the animals were returned to ad libitum access to standard pelleted chow and water. Animals were placed in a special chamber for 5 min. This chamber contained a feeder with sunflower seeds and a small amount of wood shavings. At the end of the habituation period, forced hypothalamic stimulation was applied at the same intensity (10 periods of 30 s) used during the competition test between self-stimulation and feeding behavior. Stimulation-induced feeding responses or chewing were recorded [11, 12].

Self-Stimulation-Induced Emotional Eating

Test. In the emotional overeating test conducted in satiated rats, the threshold current intensity required to maintain lever pressing during self-stimulation was used. To determine the threshold, the current intensity was adjusted in 5 μ A increments. After determination of the stimulation threshold, a feeder was placed in the Skinner chamber and the self-stimulation pedal was activated. The number of approaches to the feeder, the number of seeds eaten, the number of pedal presses at a fixed threshold current, and feeding behavior pa-

rameters were recorded over a 10-minute period. On subsequent days, the drugs were administered 20 min before testing, after which the rats were placed in the chamber to assess self-stimulation induced overeating [13, 14].

Tirzepatide (PROMOMED PJSC, Russian Federation) was used in the study. Tirzepatide was administered subcutaneously in the scruff at doses of 0.05, 0.1, and 0.3 mg/kg body weight, in a volume of 1 ml/kg, calculated individually according to body weight, for 7-day course. A sterile 0.9% sodium chloride solution served as a control solution, administered subcutaneously.

Rats were tested 20 minutes after the final administration.

Statistical processing. Statistical significance was assessed using GraphPad Prism 10. Data were tested for normality using the Shapiro–Wilk test. As the data were not normally distributed, the nonparametric Kruskal–Wallis test was used, followed by Dunn’s post hoc test and Holm’s correction. To analyze the dynamics of the parameters over time, the Friedman test was used, followed by pairwise comparisons using the Wilcoxon–Holm test. Results are presented as the median [25th; 75th percentiles], and statistical significance was set at $p < 0.05$. Additionally, the effect size (ϵ^2) and Spearman’s correlation coefficient (r_s) were calculated to assess the relationship between the number of lever presses and the amount of food consumed.

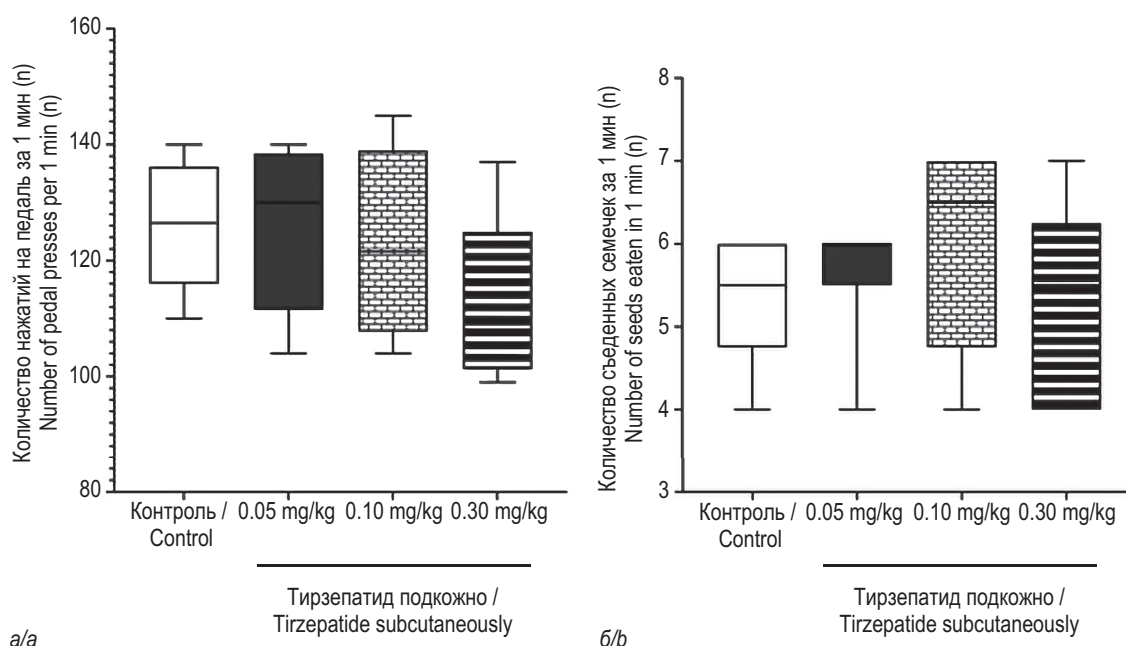


Fig. 3. Effect of tirzepatide on behavioral parameters in rats: *a* — number of pedal presses per 1 min during intracranial self-stimulation test; *b* — number of seeds eaten per 1 min. Data presented as median with 25th and 75th percentiles. Kruskal–Wallis nonparametric test followed by Dunn’s post hoc test ($p > 0.05$)

Рис. 3. Влияние тирзепатида на поведенческие показатели у крыс: *a* — количество нажатий на педаль за 1 мин при тесте самостимуляции; *б* — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскела–Уоллиса с пост-хок тестом Данна ($p > 0.05$)

RESULTS

The effects of tirzepatide on self-stimulation and feeding activity parameters were assessed 1 hour after a single subcutaneous administration of tirzepatide at doses of 0.05, 0.1, and 0.3 mg/kg.

Administration of tirzepatide within the studied dose range did not have a statistically significant effect on the number of pedal presses compared to the control group (Fig. 3, a). The activity ranged from 120 to 140 presses per minute, with no significant dose dependence.

Statistical analysis using the nonparametric Kruskal–Wallis test revealed no significant differences between groups ($H=3.5$, $p=0.38$). To clarify intergroup differences, Dunn's test was used as a post-hoc comparison, which also revealed no statistically significant differences ($p>0.05$ for all pairwise comparisons).

The effect of tirzepatide on the number of seeds consumed per minute is presented. The median values ranged from 4–7 seeds/min (Fig. 3b). A slight increase in consumption was observed at a dose of 0.1 mg/kg. However, the differences compared with the control group did not reach statistical significance. The Kruskal–Wallis test also revealed no statistically significant differences between groups ($H=2.09$, $p=0.55$). Dunn's post hoc test revealed no significant differences between individual dose groups ($p>0.05$).

Effects of tirzepatide on self-stimulation and feeding behavior on day 3 of the experiment. Behavioral testing was conducted 1 h after drug administration on day 3 of the experiment.

On day 3, a dose-dependent reduction in the number of pedal presses was observed. The most pronounced effect was observed at a dose of 0.3 mg/kg, where the median number of presses decreased by approximately 15–20% compared with the control group (Fig. 4, a).

Statistical analysis using the nonparametric Kruskal–Wallis test revealed significant differences between the groups ($H=13.69$; $p<0.001$). Dunn's post hoc test revealed that the 0.3 mg/kg tirzepatide group differed significantly from the control group ($p<0.01$). Doses of 0.05 and 0.1 mg/kg did not have a significant effect ($p>0.05$).

On day 3, a decrease in feeding activity was also observed following the administration of tirzepatide at a dose of 0.3 mg/kg (Fig. 4, b). The median number of seeds consumed per 1 min decreased compared with the control group. According to the Kruskal–Wallis test, the differences between groups were statistically significant ($H=9.64$; $p<0.05$). Dunn's post hoc test showed a significant decrease in feeding activity in the 0.3 mg/kg group compared with the control group ($p<0.05$), whereas no significant differences were observed at doses of 0.05 and 0.1 mg/kg ($p>0.05$).

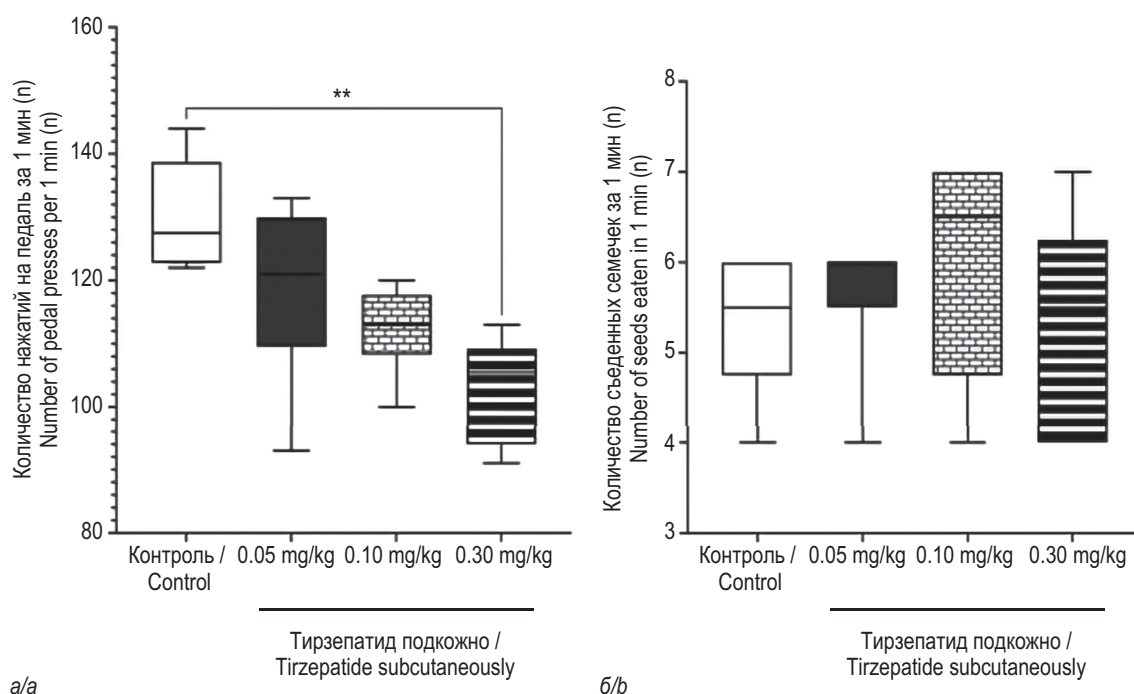


Fig. 4. Effect of tirzepatide on behavioral measures in rats on day 3 of the experiment: a — number of lever presses per 1 min in the intracranial self-stimulation (ICSS) test; b — number of seeds consumed per 1 min. Data are presented as the median and interquartile range (25th–75th percentiles). Kruskal–Wallis test with Dunn's post hoc test for pairwise comparisons. ** — $p<0.01$

Рис. 4. Влияние тирзепатида на поведенческие показатели у крыс на 3-и сутки эксперимента: а — количество нажатий на педаль за 1 мин при тесте самостимуляции; б — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскела–Уоллиса, с пост-хок тестом Данна для парных сравнений. ** — $p<0.01$

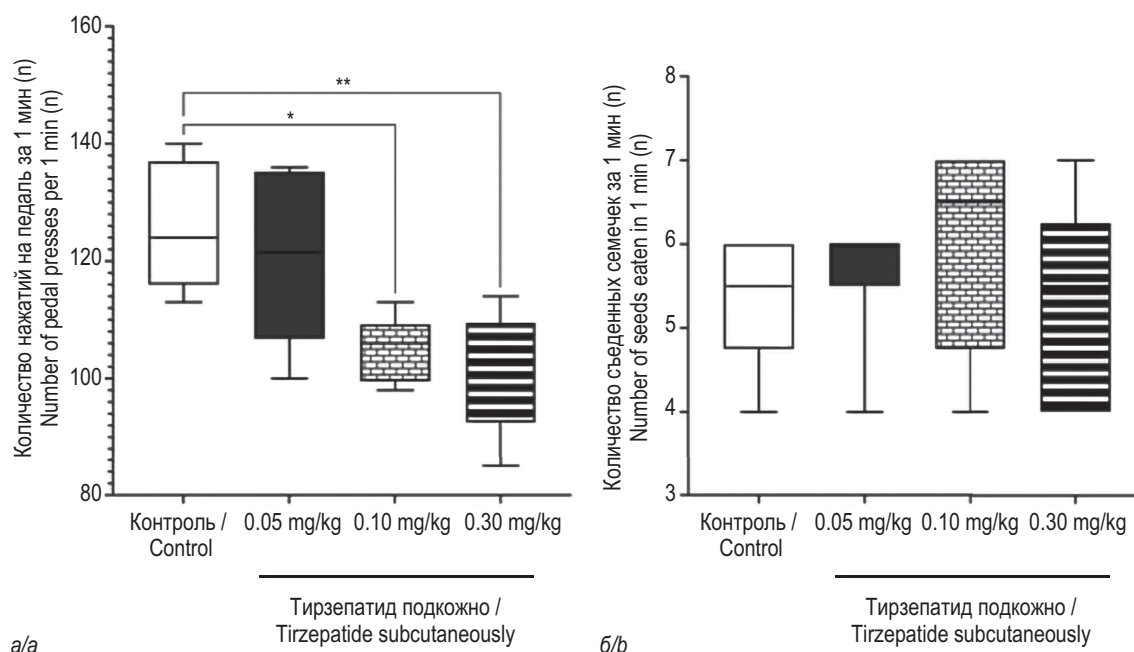


Fig. 5. Effect of tirzepatide on behavioral measures in rats on day 7 of the experiment: *a* — number of lever presses per 1 min in the intracranial self-stimulation (ICSS) test; *b* — number of seeds consumed per 1 min. Data are presented as the median and interquartile range (25th–75th percentiles). Kruskal–Wallis test with Dunn's post hoc test for pairwise comparisons. * — $p < 0.05$; ** — $p < 0.01$

Рис. 5. Влияние тирзепатида на поведенческие показатели у крыс на 7-и сутки эксперимента: *a* — количество нажатий на педаль за 1 мин при тесте самостимуляции; *б* — количество съеденных семян за 1 мин. Данные представлены в виде медианы, 25-го и 75-го процентилей. Критерий Краскала–Уоллиса с пост-хок тестом Данна для парных сравнений. * — $p < 0,05$; ** — $p < 0,01$

Effect of tirzepatide on self-stimulation and feeding behavior on day 7 of the experiment. Behavioral testing was conducted 1 h after subcutaneous administration of tirzepatide at doses of 0.05, 0.1, and 0.30 mg/kg on day 7 of the experiment. A significant dose-dependent decrease in behavioral activity was observed.

Tirzepatide administration caused a gradual decrease in lever presses, reflecting a reduction in the motivational component of behavior (Fig. 5, *a*). A moderate decrease in activity was observed at a dose of 0.05 mg/kg, while the effect was more pronounced at doses of 0.1 and 0.3 mg/kg. According to the nonparametric Kruskal–Wallis test, the differences between groups were statistically significant ($H = 13.13$; $p < 0.01$).

Additional analysis using Dunn's post hoc test showed a significant difference between the 0.1 mg/kg group and the control ($p < 0.01$) with the most pronounced decrease in the number of presses at a dose of 0.3 mg/kg ($p < 0.01$).

In parallel, the feeding behavior test also revealed a significant dose-dependent reduction in the number of seeds consumed (Fig. 5*b*). At doses of 0.1 and 0.3 mg/kg, food intake was almost halved compared to the control group. Statistical analysis using the Kruskal–Wallis test confirmed significant differences between groups ($H=14.16$; $p < 0.01$), and subsequent Dunn's test showed a significant reduction in food intake at doses of 0.10 mg/kg ($p < 0.05$) and 0.3 mg/kg ($p < 0.05$).

DISCUSSION

The study revealed that administration of tirzepatide induces pronounced dose-dependent and time-dependent changes in behavioral activity of rats. On day 1 after a single administration of the drug, no statistically significant changes were observed in the lever-pressing frequency or feeding activity, indicating the absence of an immediate effect on the reward system and food motivation. However, by day 3 of the experiment, a significant decrease in the number of lever presses in the self-stimulation test, along with the reduction in seed consumption, was observed at the dose of 0.3 mg/kg. On day 7, a persistent and pronounced dose-dependent decrease in both motivational activity and feeding behavior was observed, with significant differences found for the 0.1 and 0.3 mg/kg doses compared to the control group. These results confirm the cumulative effect of tirzepatide and its ability to gradually modulate behavioral patterns associated with the reward system.

The obtained data reflect both the peripheral and central action of the drug [15]. Tirzepatide is a dual agonist of GLP-1R and GIPR, allowing it to simultaneously activate two incretin pathways. Peripherally, tirzepatide slows gastric emptying, reduces intestinal motility, and enhances satiety signals, leading to decreased food intake [16]. However, much more interesting are the central effects mediated by GLP-1R activation in brain structures involved in reward and

motivation regulation. GLP-1-producing neurons in the nucleus tractus solitarius (NTS) are known to project to the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, and hippocampus — areas involved in the regulation of dopaminergic reinforcement [17, 18]. Activation of GLP-1R in these regions suppresses dopaminergic activity, reducing the attractiveness of rewarding stimuli and diminishing motivationally driven behavior [19, 20]. These mechanisms may explain the observed decrease in self-stimulation frequency, which is a model for assessing dopaminergic activity and positive reinforcement.

The observed anorexigenic effect of tirzepatide is consistent with known data on the role of GLP-1 in the regulation of appetite and energy metabolism [21]. Stimulation of GLP-1R in the hypothalamus and brainstem has been shown to enhance satiety and reduce food cravings, as supported by data from both experimental models and clinical observations [4]. Concurrent activation of GIPR can enhance or prolong these actions through synergistic effects on pancreatic β -cells and modulation of peripheral metabolism. Thus, the combined activation of GLP-1R and GIPR generates a more stable and potent regulatory response at both the level of glucose homeostasis and within the reward system [10].

The temporal profile of the drug's action deserves special attention. The absence of an effect after a single administration and its gradual increase by days 3 and 7 indicate the cumulative nature of tirzepatide's action. This may be due to the pharmacokinetic properties of the drug, including a long half-life and a gradual increase in concentration with repeated injections, as well as to the gradual restructuring of neuronal circuits [22]. Repeated activation of GLP-1R can induce plastic changes in dopaminergic synapses, reducing the sensitivity of the mesolimbic system to external reward stimuli [23]. From a functional point of view, this is manifested as a decrease in motivational activity, reflected by a reduced number of lever presses in the ICSS, as well as a decrease in spontaneous food intake, indicating suppression of behavioral responses associated with positive reinforcement.

These data are consistent with the current understanding of the incretin system as a neurometabolic regulator integrating energy balance and motivational behavior [24]. A number of studies have shown that GLP-1R agonists (liraglutide, semaglutide) reduce both body weight and appetite and the desire to consume psychoactive substances and alcohol, which is explained by a common effect on the mesolimbic dopaminergic system. In this context, tirzepatide, which combines GLP-1R and GIPR activation, may have similar but more pronounced effects, making it a

promising agent for treatment of obesity, diabetes, as well as for the modulation of impulsive and addictive behavior [15, 25, 26].

Thus, the results of this study demonstrate that repeated administration of tirzepatide leads to a consistent and statistically significant reduction in operant behavior and food intake in rats. The effect is dose-dependent and increases over time, reflecting both the peripheral (metabolic) and central (neuromodulatory) mechanisms of the drug's action.

The reduction in lever pressing and food intake can be viewed as a behavioral equivalent of decreased reward motivation and appetite, consistent with the known properties of incretin receptor agonists. These data confirm the involvement of GLP-1/GIP-dependent mechanisms in the regulation of the reward system and open up the prospect of further study of tirzepatide as a therapeutic agent for the treatment of motivational and impulsive behavior disorders.

CONCLUSION

Repeated administration of the dual incretin receptor agonist tirzepatide induces a pronounced dose- and time-dependent reduction in motivational and food-directed activity in rats, indicating the involvement of GLP-1/GIP-dependent neuromodulatory mechanisms in the regulation of motivational-reinforcement processes (reward system) and the control of feeding behavior. This supports the potential of tirzepatide as a therapeutic agent for the correction of disorders associated with impulsive and addictive behavior.

ADDITIONAL INFORMATION

Author contributions. All authors made a significant contribution to the conception, design, execution, and interpretation of the study, read, and approved the final version of the manuscript before publication.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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Ethics expertise. The study was approved by the Local Ethics Committee of Saint Petersburg State Pediatric Medical University, protocol No. 58/03 dated September 25, 2025.

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU

of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведении исследования и подготовки статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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FGWG-2025-0020 «Поиск молекулярных мишеней для фармакологического воздействия при аддитивных и нейроэндокринных нарушениях с целью создания новых фармакологически активных веществ, действующих на рецепторы ЦНС».

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Calcium and fluoride hygiene products in remineralization of teeth enamel of young and elderly people

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ABSTRACT

Background. Based on the composition of toothpaste, dentists and dental hygienists provide recommendations to patients on the choice of toothpaste, depending on the presence of dental pathology. At the same time, a comparative assessment of the use of calcium and fluoride toothpastes in adults, taking into account their age, has not yet been studied.

The purpose of this study is to investigate the effectiveness of tooth enamel remineralization in young and elderly patients using calcium and fluoride toothpaste.

Material and methods. The study involved 80 people, of which 40 were in the young age group (19–43 years old) and 40 were in the elderly age group (61–74 years old). Based on the purpose of the study, three research groups were formed. After the initial dental examination and professional oral hygiene, the subjects of the control group performed individual oral hygiene with their usual toothpastes. The second and third groups (young and elderly people) performed individual oral hygiene using a calcium-containing toothpaste with hydroxyapatite or a fluoride-containing toothpaste with a fluoride ion content of 1450 ppm. The functional resistance of tooth enamel was assessed twice: at the initial visit to the dentist and 45 days after the initial examination. The enamel resistance test (TER test) was used to determine the dynamics of tooth enamel resistance.

Results. It was found that patients of all groups had a high level of caries resistance during the clinical study. In young people, the effectiveness of using calcium-containing and fluoride-containing toothpaste in terms of remineralization was the same. For older people, regular use of fluoride-containing toothpaste for 45 days was 14.27% more effective than calcium-containing toothpaste.

Conclusion. The use of calcium and fluoride toothpastes by young people increases enamel mineralization by 17.54 and 15.49%, respectively, over a period of 45 days. In contrast, the use of calcium and fluoride toothpastes by older patients increases enamel mineralization by 7.24 and 21.52%, respectively, over the same period of time. For young people living in regions with low fluoride levels, it is advisable to use calcium-containing toothpastes daily. For older people, fluoride-containing toothpastes are recommended.

Keywords: young people, elderly people, teeth, tooth enamel, tooth enamel resistance, oral hygiene, toothpaste, Saint Petersburg

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Кальциевые и фтористые средства гигиены в реминерализации эмали зубов у молодых и пожилых людей

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РЕЗЮМЕ

Актуальность. Выбор зубной пасты обычно производится в зависимости от наличия или отсутствия стоматологической патологии. В то же время до сих пор не дана сравнительная оценка использования кальциевых и фтористых зубных паст у взрослых людей с учетом их возраста.

Цель исследования — изучить эффективность реминерализации эмали зубов у молодых и пожилых пациентов с применением кальциевой и фтористой зубных паст.

Материалы и методы. В исследовании приняло участие 80 людей: 40 молодых (19–43 года) и 40 человек пожилого возраста (61–74 года). Испытуемые контрольной группы после первичного стоматологического осмотра и профессиональной гигиены полости рта осуществляли индивидуальную гигиену с обычными для них зубными пастами. Вторая и третья группы (молодые и пожилые люди) проводили индивидуальную гигиену рта с помощью кальцийсодержащей зубной пасты с гидроксиапатитом или фтористой пасты с содержанием фторид-иона 1450 ppm. Оценку функциональной резистентности эмали зубов проводили дважды: при первичном обращении пациентов к стоматологу, а также через 45 суток от первичного осмотра. Для определения динамики резистентности эмали зубов применяли тест эмалевой резистентности (ТЭР-тест).

Результаты. У пациентов всех групп на протяжении клинического исследования отмечен высокий уровень кариесрезистентности. У молодых людей эффективность от применения в аспекте реминерализации кальцийсодержащей и фтористой зубных паст была одинакова. Для людей пожилого возраста регулярное применение фтористой зубной пасты на протяжении 45 суток было эффективнее кальцийсодержащей на 14,27%.

Выводы. Применение кальциевой и фтористой зубных паст молодыми людьми повышает минерализацию эмали за 45 суток соответственно на 17,54 и 15,49%, в то время как у пожилых пациентов кальциевые и фтористые зубные пасты повышают минерализацию эмали за аналогичный период времени соответственно на 7,24 и 21,52%. Для молодых людей, проживающих в регионах с пониженным содержанием фторид-иона, целесообразно ежедневно применять кальцийсодержащие зубные пасты, а людям пожилого возраста — фтористые зубные пасты.

Ключевые слова: молодые люди, пожилые люди, зубы, эмаль зуба, резистентность эмали зуба, гигиена полости рта, зубная паста, г. Санкт-Петербург

Как цитировать

Музыкин М.И., Иорданишвили А.К. Кальциевые и фтористые средства гигиены в реминерализации эмали зубов у молодых и пожилых людей. *Педиатр*. 2025;16(5):56–61. <https://doi.org/10.56871/PED.2025.88.12.006>.

INTRODUCTION

Currently, a wide range of toothpastes is available for adults of all ages, differing in composition and various effects on the organs and tissues of the oral cavity [1, 2]. Based on toothpaste composition, dentists and dental hygienists provide patients with recommendations for selecting toothpaste depending on the presence of dental pathology: dental caries, inflammatory periodontal diseases, dentin hypersensitivity, dry mouth syndrome, etc. [3, 4]. Maintaining and increasing the functional resistance of dental enamel is important for adults of all ages [5–7]. At the same time, a comparative assessment of the effectiveness of calcium-containing and fluoride toothpastes in adults, taking age into account, has not yet been conducted.

AIM

The aim of this study was to evaluate the effectiveness of enamel remineralization in young and elderly patients depending on the use of calcium- or fluoride-containing toothpastes.

MATERIALS AND METHODS

The study involved 80 participants, of whom 40 belonged to the young age group (19–43 years) and 40 to the elderly age group (61–74 years). Three study groups were formed. The first (control) group was divided into two subgroups according to age. Subgroup 1A consisted of young individuals, and subgroup 1B consisted of elderly individuals. After an initial dental examination and professional oral hygiene

procedures, these patients performed individual oral care using their usual toothpaste.

The second group consisted of young people. Half of this group (2A) was advised to perform individual oral hygiene using a calcium-containing toothpaste with hydroxyapatite, and the other half was advised to use a fluoride toothpaste with a fluoride ion content of 1450 ppm.

The third group consisted of elderly individuals. Half of these individuals (Group 3A), as in the second study group, were advised to perform individual oral hygiene with a calcium-containing toothpaste with hydroxyapatite, while the other half were advised to use a fluoride toothpaste containing 1450 ppm fluoride ions. The distribution of patients by gender within the groups is shown in Figure 1.

The groups included only patients with satisfactory oral hygiene, at least 20 natural teeth in both jaws that were not covered by artificial crowns, and compensated dental caries (DMFT index (Decayed, Missing, and Filled Teeth) did not exceed 5). All patients included in the study were born in St. Petersburg, reside there, and used tap water for drinking. All patients underwent professional oral hygiene before the start of the study. Patients in the second and third study groups were recommended exclusively domestic calcium-containing and fluoride toothpastes, respectively. The functional resistance of tooth enamel was assessed twice: at the initial visit and again 45 days after the initial examination. The TER test was used to evaluate changes in tooth enamel resistance over time [8].

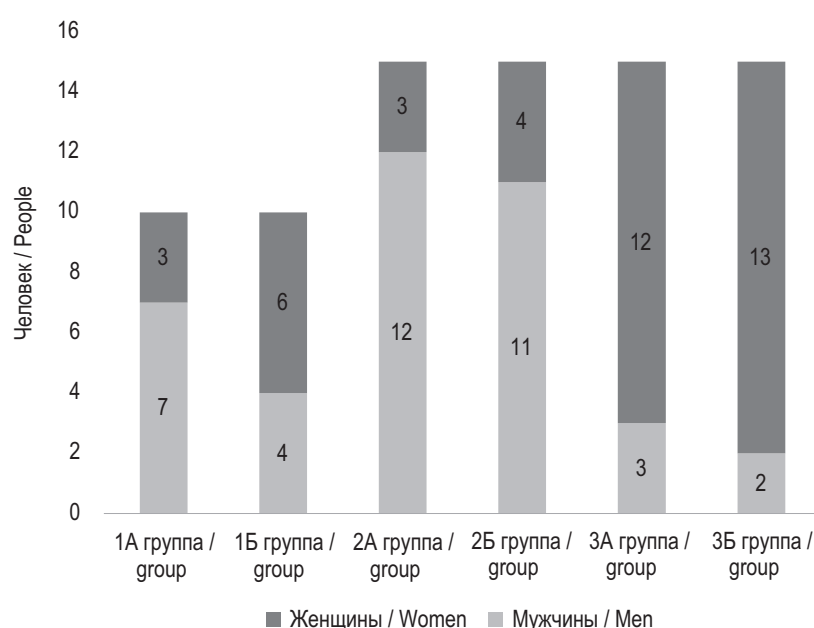


Fig. 1. Distribution of patients in the study groups by age, sex and toothpaste type

Рис. 1. Распределение пациентов в группах исследования с учетом возраста, пола и типа пасты

The study fully complied with the ethical standards of the Committee on Human Experimentation, the 1975 Helsinki Declaration and its 2000 revision.

Statistical analysis was performed using the standard software package STATISTICA for Windows, version 7.0. The significance level for testing the null hypothesis (absence of significant differences or factor effects) was set at $p < 0.05$.

RESULTS AND DISCUSSION

Evaluation of tooth enamel resistance in the control group showed that, at the baseline, the functional enamel resistance in young and elderly people was 2.09 ± 0.19 and 2.20 ± 0.18 conventional units ($p \leq 0.05$), respectively. After 45 days, there were no statistically significant differences in the enamel resistance indicators. In young and elderly people, the functional enamel resistance was 2.10 ± 0.17 and 2.19 ± 0.19 conventional units ($p \leq 0.05$), respectively. Throughout the study, all patients in the control group demonstrated a high level of caries resistance (Fig. 2).

At the beginning of the study, the assessment of tooth enamel resistance in patients of the second group showed that, in young people, the functional enamel resistance was 2.11 ± 0.18 conventional units in subgroup 2A and 2.13 ± 0.19 conventional units in subgroup 2B ($p \leq 0.05$). After 45 days, statistically significant changes in the enamel resistance indices were observed in both subgroups 2A and 2B. Thus, in young people of subgroup 2A, the TER test value was 1.74 ± 0.18 conventional units, and in patients of

group 2B it was 1.82 ± 0.19 conventional units. This indicates a positive trend in the degree of tooth enamel mineralization ($p \leq 0.05$).

In elderly patients of the third group, the indices of functional resistance of enamel were 2.21 ± 0.19 in subgroup 3A and 2.23 ± 0.17 conventional units in subgroup 3B ($p \leq 0.05$), respectively. After 45 days, a significant positive improvement in functional enamel resistance was registered only in subgroup 2B, where elderly patients used fluoride toothpaste; the index was 1.75 ± 0.17 ($p \leq 0.05$). In elderly patients of subgroup 3A, who used calcium-containing toothpaste, a positive trend in enamel mineralization was also noted, since at the end of the study, their TER test index was 2.05 ± 0.18 (Fig. 2). It should be noted that patients in the second and third study groups, as well as those in the first group, demonstrated a high level of caries resistance throughout the study, regardless of age.

The data obtained indicate that young and elderly individuals with satisfactory oral hygiene demonstrated high levels of caries resistance despite low fluoride concentrations in drinking water. In young adults, regular use of hydroxyapatite and fluoride toothpastes resulted in improved enamel mineralization. No significant differences were found in the final TER test results, demonstrating the effectiveness of both calcium-containing and fluoride toothpastes used for daily oral hygiene. For elderly patients, fluoride toothpaste was more effective in terms of tooth enamel mineralization: it remineralized enamel 14.27% better (with an observed increase in enamel mineralization of 21.52%) than calcium-containing toothpaste, which resulted in an increase in enamel mineralization of 7.24%.

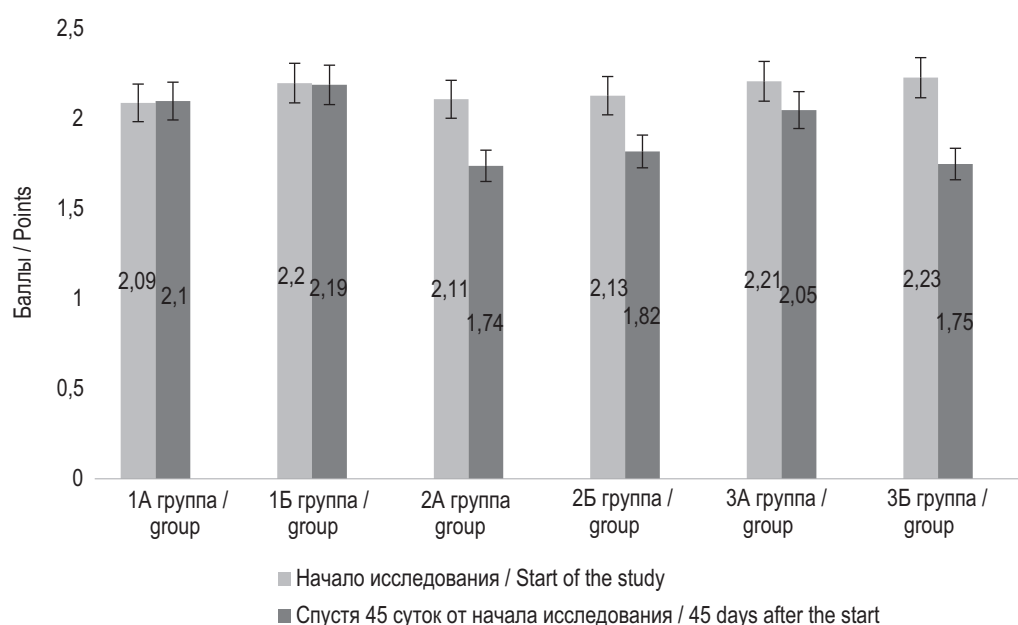


Fig. 2. Characteristics of the functional resistance of tooth enamel in patients during the study, points

Рис. 2. Характеристика функциональной резистентности эмали зубов у пациентов в ходе проведенного исследования, баллы

CONCLUSION

1. In young adults, the use of calcium-containing and fluoride toothpastes increased enamel mineralization by 17.54% and 15.49%, respectively, over 45 days, while in older adults, calcium-containing and fluoride toothpastes increased enamel mineralization by 7.24% and 21.52%, respectively, over the same period.

2. For young adults living in regions with low fluoride levels in drinking water, daily use of calcium-containing toothpastes is recommended, while fluoride toothpaste is recommended for older adults. This approach may improve the caries resistance of natural teeth and optimize dental health of adults of all ages.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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The influence of exercises with a temporal structure of movements on the development of coordination abilities in primary school children

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ABSTRACT

Background. During the period of primary school age, there is a peak in the development of coordination abilities. The development and implementation of new exercise programs, the use of specialized devices and innovative methods is an urgent task for further improvement of coordination.

Aim. The aim is to evaluate the impact of exercises with a temporal structure of movements on the components of coordination abilities in primary school children.

Materials and methods. The participants of the experiment were children of primary school age (8–9 years old). The experiment consisted of two stages: a four-week one (classes were conducted according to the standard curriculum) and a six-week one, where participants performed a developed program of exercises with a time-based structure of movements on a coordination ladder. The organization of the two stages of the study included classes lasting 30 minutes with a frequency of 3 times a week. Two-time testing (T) was performed at the beginning (T1) and the end (T2) of the second stage. The following tests were used: "Shuttle running: 3×10 m", "Tandem walking", "Walking backwards", "Sensitized Romberg test". To determine the statistical significance of the differences between the indicators, the Student's t-test was chosen. The results were considered statistically significant at $p < 0.01$.

Results. Positive dynamics was revealed in all tests. A general and differentiated assessment of the results was carried out. The difference between the averages was: The test "Shuttle running: 3×10 m, s", T1 — 11.8 ± 0.5 and T2 — 10.1 ± 0.1 amounted to 13.4%; "Tandem walking, cm/s", T1 — 27.2 ± 2.3 and T2 — 30.1 ± 2.8 amounted to 9.6%, "Walking backwards, cm/s" T1 — 56.0 ± 2.2 and T2 63.9 ± 4.9 was 12.3%, "Sensitized Romberg sample, s" T1 — 17.1 ± 0.7 and T2 — 18.1 ± 0.8 amounted to 5.5%.

Conclusions. The results of the study confirm that exercises with a temporal structure of movements have a positive effect on the components of coordination abilities in children of primary school age. The differentiated effect of these exercises on dynamic and static coordination parameters has been established.

Keywords: primary school age, coordination abilities, tempo-rhythmic structure of movements, agility ladder

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Влияние упражнений с темпоритмовой структурой движений на развитие координационных способностей у детей младшего школьного возраста

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РЕЗЮМЕ

Актуальность. В период младшего школьного возраста наблюдается пик развития координационных способностей. Разработка и внедрение новых программ упражнений, использование специализированных устройств и инновационных методов представляется актуальной задачей для дальнейшего совершенствования координации.

Цель — провести оценку воздействия упражнений с темпоритмовой структурой движений на компоненты координационных способностей у детей младшего школьного возраста.

Материалы и методы. Участники эксперимента — дети младшего школьного возраста (8–9 лет). Эксперимент состоял из двух этапов: контрольный (4 недели, сентябрь) — занятия по стандартной учебной программе; экспериментальный (8 недель, октябрь–ноябрь) — программа с использованием упражнений с темпоритмовой структурой движений на координационной лестнице. Продолжительность занятия составляла 30 минут, частота — 3 раза в неделю. Тестирование проводилось дважды: на старте (Т1) и по завершении (Т2) второго этапа. Использованы тесты «Челночный бег 3×10 м», «Тандемная ходьба», «Ходьба спиной вперед», «Модифицированная проба Ромберга». Статистическая значимость различий оценивалась с использованием t-критерия Стьюдента для парных выборок при уровне значимости $p < 0,01$.

Результаты. По всем тестам зафиксирована положительная динамика. Проведена общая и дифференцированная оценка результатов. Разница между средними значениями: тест «Челночный бег 3×10 м, с» Т1 — $11,8 \pm 0,5$ с и Т2 — $10,1 \pm 0,1$ с, улучшение на 13,4%; «Тандемная ходьба» Т1 — $27,2 \pm 2,3$ см/с и Т2 — $30,1 \pm 2,8$ см/с, прирост 9,6%; «Ходьба спиной вперед, см/с» Т1 — $56,0 \pm 2,2$ см/с и Т2 — $63,9 \pm 4,9$ см/с, увеличение на 12,3%; «Модифицированная проба Ромберга» Т1 — $17,1 \pm 0,7$ с и Т2 $18,1 \pm 0,8$ с составила рост на 5,5%.

Выводы. Результаты исследования подтверждают, что упражнения с темпоритмовой структурой движений оказывают положительное воздействие на компоненты координационных способностей у детей младшего школьного возраста. Установлено дифференцированное влияние данных упражнений на динамические и статические параметры координации.

Ключевые слова: дети младшего школьного возраста, координационные способности, темпоритмовая структура движений, координационная лестница

Как цитировать

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BACKGROUND

In the context of modern education, school physical education classes play a key role in the development of motor abilities in primary school children [11].

Motor skills are fundamental elements of a child’s physical development. They determine a child’s ability to actively participate in a variety of activities and adapt to changing environmental conditions [3, 14, 17, 23].

Insufficient development of fundamental motor skills during childhood can lead to musculoskeletal disorders. This is due to the immaturity of the central nervous system, which is responsible for coordinating muscle activity and movement patterns [1, 7, 10, 16].

Coordination is the process of achieving coordinated muscle activity required to perform new motor actions. It represents a complex of abilities comprising three key components: precise control of the temporal, spatial, and dynamic parameters of movements; maintenance of static and dynamic balance; and the execution of motor actions with optimal muscular tension [19]. The sensitive period for the development of coordination abilities is between the ages of 6 and 12 years [8, 18]. During this period, improvements in the precision and expressiveness of children’s movements are observed.

Research on the development of coordination in primary school children within educational settings shows that physical education teachers employ various methods for selecting exercise programmes and instructing their implementation [3, 9, 13]. The authors emphasize the need to revise and optimize approaches to coordination training, utilizing innovative methods [2, 6, 15, 22].

Nevertheless, the level of coordination abilities achieved through specialized methods has not been sufficiently studied. An analysis of the literature indicates that the use of agility ladder exercises and me-

thods incorporating musical accompaniment for movements is rare in practice [4, 5, 12, 20, 21].

Addressing this gap, an exercise programme with a tempo-rhythmic structure of movements was developed and tested within this study. A key element was the use of agility ladder exercises combined with rhythmic music, in which the beat tempo was progressively increased.

AIM

The aim of this study was to evaluate the effects of exercises with a tempo-rhythmic movement structure on the components of coordination abilities in primary school children.

MATERIALS AND METHODS

The study was conducted in a secondary school in St. Petersburg equipped with a sports hall. In accordance with the principles of confidentiality, the name of the school and participants’ data were not disclosed. During the preparatory phase, meetings were held with parents and teachers to explain the aims, objectives, and procedures of the study.

The effectiveness of the programme was evaluated between September and December. The study involved 20 primary school children aged 8–9 years, including 10 boys and 10 girls. Participants were selected based on anthropometric data (Table 1) and baseline physical fitness test results (Table 2). The tests included the following exercises: sit-ups (number of repetitions per minute) and squats (number of repetitions per minute).

Statistical analysis revealed no significant differences between boys and girls in age, anthropometric parameters (height, body weight, body mass index, and foot length), or physical fitness indicators (less than 1%). On this basis, a single sample was formed without stratification by sex.

Table 1. Anthropometric indicators of the study participants based on testing results, M±m

Таблица 1. Антропометрические показатели участников исследования по результатам тестирования, M±m

Группа / Group	Возраст, мес / Age, mon	Рост, см / Height, cm	Масса тела, кг / Weight, kg	Индекс массы тела, кг/м ² / Body mass index, kg/m ²	Длина стопы, см / Foot length, cm
Мальчики / Boys (n=10)	98,2±4,2	129,7±3,7	27,8±2,4	16,2±0,2	22,4±0,8
Девочки / Girls (n=10)	99,8±4,8	128,0±4,4	27,4±1,9	16,5±0,6	21,8±0,9

Table 2. Physical indicators of participants according to testing results, M±m

Таблица 2. Физические показатели участников по результатам тестирования, M±m

Группа / Group	Поднимание туловища за 30 с / Sit-ups (30 s)	Приседания за 1 мин / Squats (1 min)
Мальчики / Boys (n=10)	13,3±0,5	30,8±0,7
Девочки / Girls (n=10)	14,5±0,7	31,1±0,8

Table 3. Parameters of the organization and content of the control and experimental stages of the pedagogical experiment**Таблица 3.** Параметры организации и содержания контрольного и экспериментального этапов педагогического эксперимента

Параметр / Parameter	Контрольный этап / Control phase	Экспериментальный этап / Experimental phase
Период / Period	Сентябрь / September	Октябрь, ноябрь / October, November
Продолжительность / Duration	4 недели / 4 weeks	8 недель / 8 weeks
Содержание / Program content	Стандартная программа / Standard curriculum	Упражнения с темпоритмической структурой движений / Tempo-rhythmic exercises
Оборудование / Equipment	Базовое спортивное оборудование / Basic sports equipment	Координационная лестница / Agility ladder

The study was conducted in two stages (Table 3). During the first stage (4 weeks), the standard physical education curriculum for second-grade students was implemented¹. This programme was aimed at developing fundamental motor skills and physical qualities, including coordination abilities. The main directions for coordination development were developing spatial orientation, improving rhythm perception, training static and dynamic balance, and refining movement differentiation.

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The second stage of the study, lasting 8 weeks, involved the implementation of the developed exercise programme. The methodology included exercises using an agility ladder with the following dimensions: length (L) — 4 m and width (W) — 50 cm.

Three main types of movements were performed on the agility ladder: walking, running, and jumping. The sessions were conducted to rhythmic music at a tempo of 96–112 bpm. The tempo-rhythmic structure of the exercises allowed for individual adjustments to movement technique based on the participants' abilities.

The following standardised tests were used to assess coordination abilities.

1. "Shuttle run 3×10 m". This test assessed dynamic coordination. It involved repeated covering of the distance with changes of direction; the results were recorded in seconds.

2. "Tandem walking". This test was used to assess gait function with complex coordination. Participants walked 5 m along a straight line, placing one foot in a heel-to-toe position; the results were recorded in cm/s.

3. "Backward walking". This test was used to assess mobility and balance maintenance. Participants walked backwards along a line while looking over the right shoulder in the direction of movement; the results were recorded in cm/s.

4. "Modified Romberg test". This test is an indicator of static coordination. Participants assumed a tandem stance (heel-to-toe position) with their arms crossed on the chest; the maximum time for maintaining the position is recorded.

During the study, participants performed the tests. Testing began with a practice attempt, followed by repeated trials until a satisfactory (verifiable) result was achieved. The dynamics of coordination ability development were analysed and expressed as percentages. The results of the "Shuttle run 3×10 m" and "Modified Romberg test" were compared with normative reference values for children aged 6–7 years based on monitoring data². Statistical processing was performed using SPSS 16.0. The paired-sample t-test was used to assess the statistical significance of differences. The level of statistical significance was set at $p < 0.01$.

RESULTS

A comparative analysis of the results was conducted to evaluate the effectiveness of training programme: baseline measurements (T1) were compared with those obtained after the 8-week course of sessions (T2) (Table 4). The programme consisted of exercises with a tempo-rhythmic movement structure performed on an agility ladder and accompanied by music with a progressively increasing tempo.

A comparative analysis of the control exercise results revealed a statistically significant improvement in the participants' physical performance. In the

¹ Work Programme for the Academic Subject «Physical Education» for Grades 1–4 of Primary General Education for the 2023–2024 Academic Year. Available at: <https://co8a.ru/wp-content/uploads/2023/08/1-1.pdf> (accessed: 08.02.2025).

² Educational Social Network. Normative Indicators for Monitoring. Available at: <https://nsportal.ru/shkola/raznoe/library/2016/03/15/normativy-pokazateley-monitoringa> (accessed: 08.02.2025).

Table 4. Dynamics parameters of physical fitness and coordination abilities in the subjects before (T1) and after (T2) the experiment, $M \pm m$ **Таблица 4.** Динамика показателей физической подготовленности и координационных способностей у испытуемых до (T1) и после (T2) эксперимента, $M \pm m$

Показатели / Parameters	T1 (n=20)	T2 (n=20)
Упражнения / Exercise		
Подъем туловища (раз/мин) / Sit-ups (count/min)	21,3 $\pm$ 1,5	24,2 $\pm$ 1,1*
Приседания (раз/мин) / Squats (count/min)	35,8 $\pm$ 2,8	38,5 $\pm$ 1,9*
Тесты / Tests		
Челночный бег 3 $\times$ 10 м, с / Shuttle run 3 $\times$ 10 m, s	11,8 $\pm$ 0,5	10,1 $\pm$ 0,1*
Тандемная ходьба, см/с / Tandem walk, cm/s	27,2 $\pm$ 2,3	30,1 $\pm$ 2,8*
Ходьба спиной вперед, см/с / Backward walk, cm/s	56,0 $\pm$ 2,2	63,9 $\pm$ 4,9*
Тест «Модифицированная проба Ромберга», с / Modified Romberg Test, s	17,1 $\pm$ 0,7	18,1 $\pm$ 0,8*

* Differences are significant at the level of significance ($p < 0,001$).* Различия достоверны на уровне значимости ($p < 0,001$).

“sit-ups” test, the mean number of repetitions increased by 3 (+11.9%). Similar dynamics were observed in the “squats” exercise, where the number of repetitions increased by a mean of 3 (+7.1%).

The results of the “shuttle run 3 $\times$ 10 m” test showed a 13.4% improvement compared with baseline data. This corresponded to a 1-point increase on a 3-to-4-point scale.

Analysis of data from the “tandem walking”, “backward walking”, and “modified Romberg test” revealed positive dynamics across all results. The mean speed in the “tandem walking” and “backward walking” tests increased by 9.6 and 12.3%, respectively. The difference between the results of the “modified Romberg test” was 5.5%, which also corresponds to a 1-point increase from 3 to 4.

A comparative analysis of the changes observed across the four coordination ability tests revealed specific patterns. The use of exercises with a tempo-rhythmic movement structure using the agility ladder had a pronounced effect on the development of dynamic coordination. This is supported by the greatest improvements being observed in the “shuttle run” test (a 1.7-second decrease in time) and the “backward walking” test (a 2.9 cm/s increase in speed), indicating a significant enhancement of motor adaptation ability.

CONCLUSION

The results of the study confirm the effectiveness of tempo-rhythmic exercises in the development of coordination abilities in primary school children ($p < 0.001$). However, differential patterns of improvement were observed depending on the type of motor task.

The observed increase in the number of repetitions in the sit-ups and squats exercises may be associated with the development of endurance under the

influence of the increasing tempo of the agility ladder exercises. The greatest progress was observed in tests assessing dynamic coordination and motor control (shuttle run 3 $\times$ 10 m and backward walking). This result is presumably a consequence of synchronising cyclic movements with the musical tempo. The improvement in the tandem walking and modified Romberg test results was less pronounced, as the skills assessed require a high level of precision and static stability. These parameters of motor control, unlike cyclic movements, develop more slowly and are less responsive to musical rhythm.

Thus, exercises with a tempo-rhythmic movement structure contribute to the development of coordination abilities by improving both complex coordinated movements (reaction time and movement speed) and static parameters (movement precision and postural maintenance). This conclusion is supported by the test results obtained from primary school children in this study.

ADDITIONAL INFORMATION

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение ис-

следования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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Electroneuromyography in pediatric practice (literature review)

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ABSTRACT

One of the most informative diagnostic methods for diseases of the spinal cord and peripheral nervous system is electromyography, a diagnostic technique based on the registration and evaluation of electrical potentials that occur during muscle contraction or peripheral nerve activation in response to electrical stimulation of the nerves. This method is characterized by high variability in the obtained potential parameters: amplitude, latency, morphology, the ratio of these parameters between responses recorded at different stimulation points, as well as conduction velocities along motor and sensory fibers of peripheral nerves. The performance of electromyography in children is associated with several additional complicating factors, such as the high sensitivity of children to the procedures, the difficulty in ensuring patient immobility, and the dependence of the obtained data on the age of the subject. This study involved a review of recent domestic and international literature on the use of electromyography in pediatric practice. Currently, two main electrophysiological methods are used: stimulation electromyography and needle electromyography. In the first case, the conduction of signals along peripheral nerves is assessed, while in the second, the condition of individual muscle fibers is evaluated. During the examination, diseases of the muscles, peripheral nervous system, and spinal cord can be identified; it is also possible to compare the obtained results to assess inter-lateral asymmetry and track the dynamics of pathological processes over time. Electromyography is a highly informative diagnostic tool for neuromuscular system diseases in children; however, when conducting the study, it is important to take into account the age-related features of nervous system development and adapt the procedure according to the physiological and behavioral characteristics of the subjects.

Keywords: pediatrics, electroneuromyography, needle electromyography, diabetic polyneuropathy, muscular hypotonia syndrome

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Электронейромиография в педиатрической практике (обзор литературы)

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РЕЗЮМЕ

Актуальность изучения возможностей применения электронейромиографии в педиатрической практике обусловлена широким спектром нервно-мышечных заболеваний, при которых данная методика является высокоспецифичной и информативной. Электронейромиография — это один из наиболее информативных методов диагностики заболеваний спинного мозга и периферической системы. Метод основан на регистрации и оценке электрических потенциалов, возникающих при сокращении мышцы или активации периферического нерва в ответ на стимуляцию нервов электрическими импульсами. Электронейромиография отличается высокой вариабельностью показателей полученных потенциалов: их амплитуды, латентности, морфологии, соотношения данных показателей между ответами, полученными в различных точках стимуляции, а также скоростей проведения по моторным и сенсорным волокнам периферических нервов. Проведение электромиографии у детей сопряжено с рядом дополнительных осложняющих факторов, таких как высокая чувствительность детей к производимым манипуляциям, сложность обеспечения неподвижности пациента и зависимость полученных данных от возраста обследуемого. В ходе данного исследования был проведен анализ отечественной и зарубежной литературы последних лет на тему возможности использования электромиографии в педиатрической практике. В настоящее время используются два основных электрофизиологических метода исследования: стимуляционная электронейромиография и игольчатая миография. В первом случае оцениваются показатели проведения по периферическому нерву, во втором — состояние отдельных мышечных волокон. При проведении исследования могут быть выявлены заболевания мышц, периферической нервной системы, спинного мозга, миогенные расстройства; возможно сравнение получаемых показателей для оценки межсторонней асимметрии, динамики патологического процесса во времени. Электромиография является высокоинформативным методом диагностики заболеваний нейромышечной системы у детей, тем не менее при проведении исследований нужно учитывать возрастные особенности развития нервной системы, адаптировать проведение методики с учетом физиологических и поведенческих характеристик обследуемых.

Ключевые слова: педиатрия, электронейромиография, игольчатая электромиография, диабетическая полинейропатия, синдром мышечной гипотонии

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BACKGROUND

Electrophysiological tests, such as evoked electroneuromyography (ENMG) and needle electromyography (EMG), are used to diagnose a wide range of disorders of the muscles, peripheral nervous system, and spinal cord, including in pediatric practice. These methods offer a number of advantages, including the ability to obtain quantitative data that allow for an objective assessment of the neuromuscular system, comparison of results with age-specific norms, and monitoring changes in parameters during follow-up examinations.

In our work at the Clinical Hospital of St. Petersburg State Pediatric Medical University, we evaluated the potential for using electrophysiological examination methods in pediatric practice. An analysis of recent domestic and international literature describes the possibilities and limitations of using EMG in pediatric neurology for patients of various age groups [5, 6].

During the studies, a number of parameters can be obtained: for example, during ENMG, one can record the amplitude, duration, latency, and shape of motor and sensory responses; calculate conduction velocities along peripheral nerves; and assess the stability of late phenomena; during needle EMG, pathological spontaneous activity of muscle fibers can be identified, and the amplitude and duration of motor unit potentials, the number of turns and phases in their structure can be assessed, as well as an analysis of the interference pattern and turn-amplitude analysis can be performed at maximum contraction of the muscle under examination [3]. ENMG can be used to diagnose conditions such as mono- and polyneuropathies, myasthenia gravis, tunnel syndromes, plexopathies, neural amyotrophies, and radicular syndromes; needle EMG — for diagnosing lesions of primary muscular and denervation origin [9, 19, 27].

Despite the high diagnostic value and informative nature of the EMG method, its application in pediatric practice is associated with certain difficulties due to the physiological, anatomical, and psychological characteristics of childhood, including variability in normal values, difficulties in ensuring the child's immobility during the examination, as well as children's increased sensitivity to external manipulation.

Physiological characteristics include incomplete myelination of peripheral nerves, active synaptogenesis, and the growth, maturation, and branching of axons. The presence of a myelin sheath covering the axons of nerve fibers is necessary to achieve sufficient nerve conduction velocity. Thus, incomplete myelination accounts for the characteristics of peripheral nerve conduction velocity and the increase in response latency. As a rule, a rapid increase in

conduction velocities is observed after birth; velocity parameters reach values similar to those recorded in adult patients by approximately 3–5 years of age, while certain changes, such as bimodality (the presence of two negative peaks) in sensory responses, continue to be observed until 15–16 years of age [16, 33]. When performing needle EMG, it should be noted that in cases of primary muscle lesions, instead of the interference pattern filled with low-amplitude potentials typical in adult practice, motor unit potentials with normal or increased amplitude and reduced duration may be recorded. These changes may be associated with hypertrophied muscle fibers. Broad, high-amplitude, polyphasic potentials similar to those observed in denervation lesions may also be recorded; in such cases, attention should be paid to the presence of both broad and narrow polyphasic potentials — this feature is more characteristic of the primary muscle pattern [37].

Another important factor to consider when conducting the study is the anatomical characteristics of the patients. In studies of the adult population, the distances between the stimulation site and the recording site are fixed and standardized in accordance with international recommendations, ensuring high reproducibility of results [17, 24, 26]. In children, especially younger ones, these distances often vary due to anatomical characteristics: smaller body size, lower muscle mass, and body proportions that differ from those of adult patients. This requires a flexible approach to selecting stimulation and recording sites, as well as adjusting measurements based on age and the size of the area being examined. The lack of fixed standards for children creates additional complexity in interpreting results and requires the use of age-specific reference data. Additionally, interelectrode distances may be reduced, as may the distance between the stimulating and recording electrodes. Anatomical landmarks may be used during the study [37, 40].

It should be noted that the examination may cause pain and discomfort in the area of stimulation or needle electrode insertion. Unlike adult patients, most of whom tolerate EMG satisfactorily, unpleasant sensations may cause anxiety and motor activity in the subjects, leading to an increase in the number of recording artifacts, as well as the inability to perform procedures that require patient cooperation; furthermore, communication with young children may be impossible. When conducting the examination, it is recommended to establish rapport with the child: for example, it may be helpful to engage the child in the procedure by explaining that the sounds recorded during EMG are “muscle sounds” captured by a microphone. It is recommended to avoid terms like “needle” or “needle electrode” as they carry negative

connotations. Phrases such as “recording electrode”, “microphone”, “antenna”, or others that will be perceived more positively by the child should be used. A higher quality of the examination can be achieved if a staff member or parent present distracts the child with videos, games, or books [31]. When examining patients of preschool and younger ages, parents may be invited to be present during the procedure and hold the child in their arms; however, it is necessary to explain that the child may become anxious and cry during the examination [37]. The possibility of sedating patients should be considered, as a number of publications indicate an improvement in data quality when sedation is used [18, 25], while others show that electromyography can be performed with sufficient accuracy without sedation [22].

Thus, the recording of electrophysiological parameters presents certain challenges, and a correct interpretation of the data is essential for reaching a reliable conclusion. A number of scientific studies describe conduction parameters recorded in a population of healthy children [12, 18, 20, 38, 40], noting the high variability of the data — each individual electrophysiological laboratory is recommended to develop its own reference tables or, at a minimum, cite the source according to which the recorded values are interpreted [14, 40, 44].

The use of evoked EMG and needle EMG techniques is quite common in clinical practice. The most common form of polyneuropathy in childhood is diabetic polyneuropathy. A significant number of articles describe changes in electrophysiological parameters in children with diabetes mellitus — a disease whose prevalence is steadily increasing [8, 29]. During evoked potential studies in this population, changes such as reduced motor conduction velocities [2, 23, 30] and reduced amplitudes of motor and sensory responses [2, 7] were observed. There is a challenge in determining the scope of the examination sufficient to draw a reliable conclusion — the need to examine both motor and sensory fibers of at least one lower limb has been described, while the required number of nerves examined and the necessity of assessing nerve conduction parameters in the second lower limb and upper limbs vary [10, 15]. The literature describes a correlation between increased variability in blood glucose levels and a decrease in nerve conduction velocity [32, 41]. It has also been noted that, regardless of the duration of the disease, significantly pathological changes on ENMG are observed much less frequently than during confocal microscopy with assessment of corneal nerve fiber function. Conduction parameters in the population of children with diabetes mellitus are predominantly within the normal

range but are reduced relative to those recorded in the population of healthy children [34].

The use of ENMG is not limited to the examination of children with diabetes mellitus. The examination of patients with hereditary neuromuscular diseases, metabolic disorders, rheumatic diseases, and neuropathies includes ENMG. A number of publications from 2020 and later are devoted to myographic parameters in children who have had COVID-19 followed by the development of Guillain-Barré syndrome. In a cross-sectional study involving ENMG in 125 patients reporting complaints of respiratory failure, paralysis of the upper and/or lower extremities, and gait disturbances, it was found that Guillain-Barré syndrome is characterized by an electrophysiological pattern of axonal damage to peripheral nerves, with a predominance of reduced amplitude in motor and sensory responses. Furthermore, the axonal type of lesion was associated with a less favorable prognosis for recovery than the demyelinating type [21]. Similar findings were reported in descriptions of individual clinical cases: changes of both the axonal [13] and demyelinating types [35] were noted. In a number of cases, a multisystem inflammatory syndrome associated with COVID-19 was identified in children, in which, in addition to peripheral nervous system involvement, central nervous system involvement was noted, and psychoses and epileptic seizures were described [39].

One of the most common reasons for performing an electrophysiological examination on an infant under one year of age is neonatal brachial plexus injury, which results from overstretching of the brachial plexus nerve fibers during childbirth. This condition may manifest as either a temporary decrease in arm motor function or the development of permanent complete paralysis of the upper limb. Typically, the C₅ and C₆ roots are affected (in about 80% of cases), but in some patients the C₇ root may also be involved, and rarely the C₅–T₁ roots (pamplexopathy) [28]. Depending on the extent of brachial plexus involvement, changes may vary — from minimal deviations in conduction parameters to a complete absence of responses. A combined study using both evoked EMG and needle EMG is recommended; however, it should be noted that performing needle myography is complicated by the inability to establish productive contact with the patient. Furthermore, the predominance of unilateral lesions allows for a comparative analysis of electrophysiological parameters between the affected and healthy limbs, which, given the high variability of conduction parameters in young children, significantly improves the quality of the study [42, 43].

In the practice of a pediatric electrophysiologist, it is common to encounter cases where a young child with muscular hypotonia syndrome is referred for examination.

It should be noted that the causes of this condition can vary. Given the discomfort associated with the procedure, which causes anxiety in the patient and reduces the quality of the data obtained, it is recommended to first employ other diagnostic methods (medical history review, physical examination, imaging studies, genetic/laboratory tests) followed by the development of a strategy for performing myography [1, 4, 11, 36].

CONCLUSION

The use of EMG in pediatric practice is becoming increasingly common: the quantitative data obtained are objective and can be used to compare readings between sides, assess changes over time, and monitor the effectiveness of treatment. This method can be used in children of any age. The examination allows for the differential diagnosis of a wide range of muscular and neurological disorders.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition,

analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Principles of functioning of the immunotoxicant metabolism system. Part 2: the second and third phases of biotransformation

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ABSTRACT

Biotransformation and metabolism of immunotoxicants is a complex and multi-stage process. This part of the review is devoted to the second and third stages of biotransformation of immunotoxicants, which are classified as ecotoxicants and are drugs. In second phase, partially transformed xenobiotic molecules are conjugated with certain intracellular compounds, such as glutathione, and converted into relatively safe hydrophilic metabolites of the original xenobiotic. The review describes in detail the enzyme systems that carry out biotransformation reactions of second phase. The enzymes of this biotransformation phase ultimately allow for a significant increase in the hydrophilicity of biotransformed metabolites for their subsequent excretion from the body and carry out the final detoxification of xenobiotics, including those with immunotoxicity. The known data on the localization of various isoforms of enzymes and their substrate specificity are summarized. Some reactive products of the second phase of xenobiotic biotransformation, which may be toxic to cells, are presented.

The third phase of biotransformation is the active secretion of immunotoxicants and their metabolites into urine or bile, which is carried out by proteins belonging to the superfamily of secondary membrane-bound MFS (Major Facilitator Superfamily) transporters. Transporters of the third phase are present in many tissues, including the liver, intestines, kidneys and brain, where a barrier is provided against the penetration of xenobiotics into the body. These biomolecules play an important role in regulating the absorption, distribution and excretion of many drugs and immunotoxic xenobiotics, as well as participate in the removal of newly formed products of the second phase of biotransformation from cells.

Keywords: xenobiotics, immunotoxicants, second phase of biotransformation, third phase of biotransformation

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Принципы функционирования системы метаболизма иммунотоксикантов. Часть 2: вторая и третья фазы биотрансформации

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РЕЗЮМЕ

Биотрансформация и метаболизм иммунотоксикантов — сложный и многостадийный процесс. Данная часть обзора посвящена второй и третьей стадиям биотрансформации иммунотоксикантов, являющихся экотоксикантами и лекарственными веществами. Во второй фазе частично трансформированные молекулы ксенобиотика конъюгируются с некоторыми внутриклеточными соединениями, такими как глутатион, и превращаются в относительно безопасные гидрофильные метаболиты исходного ксенобиотика. В обзоре подробно описаны ферментные системы, осуществляющие реакции второй фазы биотрансформации. Ферменты этой фазы биотрансформации в конечном итоге позволяют значительно увеличить гидрофильность биотрансформированных метаболитов для их дальнейшей экскреции из организма и осуществляют окончательную детоксикацию ксенобиотиков, в том числе обладающих иммунотоксичностью. Обобщены известные данные по локализации различных изоформ ферментов и их субстратной специфичности. Представлены некоторые реактивные продукты второй фазы биотрансформации ксенобиотиков, которые могут быть токсичны для клеток.

Третья фаза биотрансформации представляет собой активную секрецию иммунотоксикантов и их метаболитов в мочу или желчь, которая осуществляется белками, относящимися к суперсемейству вторичных мембраносвязанных переносчиков MFS (Major Facilitator Superfamily). Транспортёры третьей фазы присутствуют во многих тканях, включая печень, кишечник, почки и мозг, где обеспечивается наличие барьера против проникновения в организм ксенобиотиков. Эти биомолекулы играют важную роль в регуляции абсорбции, распределения и экскреции многих лекарств и иммунотоксичных ксенобиотиков, а также участвуют в выведении из клеток вновь образованных продуктов второй фазы биотрансформации.

Ключевые слова: ксенобиотики, иммунотоксиканты, вторая фаза биотрансформации, третья фаза биотрансформации

Как цитировать

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INTRODUCTION

After completion of phase I biotransformation of chemical compounds, their metabolites that were not included in the metabolic pathways of oxidation or biosynthesis may undergo phase II biotransformation reactions and then excreted as conjugates into the GIT and urine [9].

The mechanisms, chemical and enzymatic reactions of phase II xenobiotic biotransformation are associated with the covalent binding of xenobiotic metabolites formed during phase I biotransformation to endogenous molecules specialized for their elimination. The result is a hydrophilic conjugate that is excreted from the body. Phase II reactions are called derivatization or conjugation reactions.

Phase II biotransformation of xenobiotics includes glucuronidation, sulfation, acetylation, methylation, glutathionylation, and binding with amino acids such as glycine, taurine, glutamic acid, as well as the transformation of epoxides into dihydriols with the participation of epoxide hydrolases. The cofactors involved in these reactions are generated during phase I metabolism, with the exception of methylation and acetylation reactions. A general overview of phase II reactions is presented in Table 1.

The main organ where the second phase of xenobiotic metabolism occurs (as in the first phase) is the liver,

but the levels of some enzymes involved in biotransformation are quite high in the GIT, gonads, lungs, brain, and kidneys [10]. Phase II reactions usually proceed much faster than phase I reactions, so the total rate of transformation and elimination of a xenobiotic depends largely on the rate at which the phase I reaction proceeds.

ENZYMATIC SYSTEMS OF THE SECOND PHASE OF BIOTRANSFORMATION OF XENOBIOTICS AND THEIR FUNCTIONAL SPECIALIZATION

Enzymes involved in the second phase of biotransformation include: uridine diphosphate glucuronyltransferase (UGT), sulfotransferase, N-acetyltransferases, glutathione-S-transferases, quinone reductases, cysteine conjugating lyases, and other enzymes.

The enzymes of this phase of biotransformation ultimately significantly increase the hydrophilicity of biotransformed metabolites for their further excretion from the body and carry out the final detoxification of xenobiotics, including immunotoxicants [4]. Most of the enzymes of the second phase of biotransformation are localized in the cytosol of cells, except for UGT, which is microsomal enzyme.

Table 2 presents the functional characteristics of the main enzymes of the second phase of xenobiotic biotransformation.

Table 1. Characteristics of the main conjugation reactions of xenobiotics [13]

Таблица 1. Характеристика основных реакций конъюгации ксенобиотиков [13]

Реакция / Reaction	Присоединяемый агент / Attachment agent	Функциональная группа ксенобиотика / Functional group of xenobiotic
А. Реакции, протекающие при участии активированных форм присоединяемых агентов / A. Reactions occurring with the participation of activated forms of attached agents		
Конъюгация с глюкуроновой кислотой / Conjugation with glucuronic acid	Уридилдифосфоглюкуроновая кислота / Uridyl diphosphoglucuronic acid	OH; -COOH; NH ₂ ; -NR ₂ ; -SH; -CH
Конъюгация с глюкозой / Conjugation with glucose	Уридилдифосфо-глюкоза / Uridyl diphospho-glucose	-OH; -SH; COOH; =NH
Сульфатирование / Sulfation	3'-фосфоаденозин-5'-фос- фоссульфат (ФАФС) / 3'-phosphoadenosine-5'-phosphosulfate (PAPS)	-OH; -NH ₂ ; -SH
Метилирование / Methylation	S-аденозилметионин / S-adenosylmethionine	-OH; -NH ₂
Ацетилирование / Acetylation	Ацетил КоА / Acetyl CoA	-OH; -NH ₂
Детоксикация цианида / Cyanide detoxification	Сульфон-сульфид / Sulfone sulfide	-CN
Б. Реакции, протекающие при участии активированных форм ксенобиотиков / B. Reactions involving activated forms of xenobiotics		
Конъюгация с глутатионом / Conjugation with glutathione	Глутатион / Glutathione	Ареноксины; эпоксиды; галогенированные алкильные и арильные углеводороды / Arene oxides; epoxides; halogenated alkyl and aryl hydrocarbons
Конъюгация с аминокислотой / Conjugation with an amino acid	Глицин; глутамин; орнитин; таурин; цистеин / Glycine; glutamine; ornithine; taurine; cysteine	-COOH

Table 2. Characteristics of the main enzymes of the second phase of xenobiotic biotransformation [11, 57]
Таблица 2. Характеристика основных ферментов второй фазы биотрансформации ксенобиотиков [11, 57]

Фермент / Enzyme	Локализация / Localization	Функция / Function
УДФ-глюкуронилтрансферазы / UDP-glucuronyl transferases	Микросомы гепатоцитов / Hepatocyte microsomes	Глюкуронирование билирубина и ксенобиотиков / Glucuronidation of bilirubin and xenobiotics
Глутатион-S-трансферазы / Glutathione-S-transferases	Цитозоль и микросомы гепатоцитов / Cytosol and microsomes of hepatocytes	Конъюгация с глутатионом / Conjugation with glutathione
N-ацетилтрансфераза / N-acetyltransferase	Цитозоль гепатоцитов / Hepatocyte cytosol	Ацетилирование ксенобиотиков / Acetylation of xenobiotics
Сульфотрансферазы / Sulfone transferases	Цитозоль гепатоцитов / Hepatocyte cytosol	Сульфатирование гормонов (тиреоидные и стероидные гормоны, катехоламины) и ксенобиотиков / Sulfation of hormones (thyroid and steroid hormones, catecholamines) and xenobiotics

ENZYMATIC GLUCURONIDATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

The enzymatic reactions of glucuronidation are carried out by a group of enzymes known as glucuronyltransferases. Glucuronyltransferases catalyze the conjugation of xenobiotics or their metabolites with glucuronic acid via UDP-glucuronyltransferase (UGT) [10, 30]. This is the main route of biotransformation of xenobiotics in many mammalian species, with the exception of the cat family. Uridine diphosphoglucuronic acid participates as a cofactor in this reaction. UGT has been identified in the endoplasmic reticulum of liver cells and other tissues (kidneys, small intestine, spleen, skin, brain, etc.).

Glucuronidation typically occurs at electron-rich nucleophilic atoms of oxygen, nitrogen, or sulfur. The substrates for UGT are molecules of chemical compounds that have carboxylic, alcohol, or phenolic functional groups (the reaction produces the corresponding O-glucuronic esters), primary or secondary amino groups (N-glucuronides are formed) or a free sulfhydryl group (S-glucuronides are formed). Glucuronic conjugates are polar compounds that are soluble in water and are readily excreted in urine or bile.

The glucuronidation of xenobiotics by liver microsomes can be stimulated by detergents, which disrupt the lipid bilayer, allowing UGT greater access to uridine diphosphate glucuronic acid. However, high detergent concentrations may inhibit UGT activity by preventing the enzyme from interacting with phospholipids.

UGT catalyzes the glucuronidation of various xenobiotics, including immunotoxicants. Chemical compounds that undergo glucuronidation include: simple and complex esters; alcohols; substances containing carboxyl, carbamoyl, thiol, carbonyl, and nitro groups. The glucuronidation of toxicants in the body is usually a component of the metabolic transformations of

xenobiotics that ensure their detoxification. However, endogenous compounds such as bilirubin, steroid and thyroid hormones can also be substrates for UGT.

In rare cases, glucuronidation can increase the toxicity of a xenobiotic. For example, aromatic amines such as 2-aminonaphthalene and 4-aminobiphenyl undergo N-hydroxylation in the liver, followed by N-glucuronidation of the N-hydroxy metabolite. N-glucuronides pass through the renal filter into the bladder cavity and are hydrolyzed to the corresponding carcinogenic N-hydroxyarylamines at acidic urine pH values. In this case, the increase in xenobiotic toxicity is secondary, and the activation of the xenobiotic glucuronidation reaction may contribute to the development of bladder cancer [14].

Glucuronidation of certain chemical compounds leads to the bioactivation of carcinogens. Glucuronides with procarcinogenic properties include N-glucuronide 4-aminobiphenyl, N-glucuronide N-acetylbenzidine, O-glucuronide-4-([hydroxymethyl]-nitrosamino)-1-(3-pyridyl)-1-butanone. During the first phase of biotransformation, oxidation occurs at the nitrogen atom, followed by conversion to N-glucuronides. Once in the intestine with bile, the conjugates are broken down by glucuronidase in the microflora and ultimately converted into highly reactive electrophiles — N-acetoxyarylamines. These compounds are thought to play a significant role in the development of colon cancer in humans [2].

FERMENTATIVE SULFATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

Along with glucuronidation reactions, the metabolites of many xenobiotics undergo biotransformation through sulfate conjugation [1]. Sulfotransferases are responsible for this stage of biotransformation and metabolism of xenobiotics. Enzymes of this group have been identified in the cells of the liver, kidneys, intestines, lungs, and brain. The cofactor for sulfate

conjugation reactions is the active form of sulfuric acid, 3'-phosphoadenosine-5'-phosphosulfate (PAPS), which is synthesized in the body from adenosine triphosphate (ATP) and inorganic sulfate. A deficiency of PAPS due to a lack of sulfate or genetic defects leading to insufficient activity of the enzymes that catalyze its formation can disrupt the processes of detoxification of both xenobiotics and the degradation of endogenous compounds [15].

Sulfate conjugation involves the transfer of a sulfate group (SO_3^-) from PAPS to a biotransformable xenobiotic [1]. The substrates of this reaction are alcohols and phenols, which are often the products of phase I biotransformation and metabolism of xenobiotics and drugs. Xenobiotics that do not require prior activation by first-phase enzymes for their effective metabolism include primary and secondary alcohols, bile acids, catechols, and some aromatic amines (e.g., aniline and 2-aminonaphthalene). Such chemical compounds are conjugated with PAPS to form the corresponding sulfamates.

N-hydroxyarylamines are also substrates for sulfotransferases. In all cases, the reaction involves a nucleophilic attack of oxygen or nitrogen atoms on the sulfur atom in PAPS with cleavage of the phosphosulfate bond. Sulfate conjugates are highly water-soluble esters of sulfuric acid, which are excreted mainly in the urine. Metabolites excreted in bile can be hydrolyzed by arylsulfatases present in the intestinal microflora, which contributes to their enterohepatic circulation.

Sulfotransferases are divided into two large groups depending on their localization: membrane-associated and cytosolic. Membrane-associated sulfotransferases are present in both the endoplasmic reticulum and lysosomes, where they are mainly involved in the metabolism of endogenous peptides, proteins, glycosaminoglycans, and lipids, but are not involved in the biotransformation of xenobiotics. Cytosolic sulfotransferases are involved in the metabolism of a large number of different xenobiotics, including drugs, as well as endogenous substrates (steroid hormones, catecholamines, eicosanoids, vitamins A and D, etc.). Some sulfate conjugates undergo further biotransformation. Sulfation promotes the catabolism of thyroxine and triiodothyronine and may determine the rate of elimination of thyroid hormones. During intrauterine development, sulfotransferases are one of the main pathways of biotransformation, since UDP-glucuronyltransferase is still inactive in the fetus until the 20th week [15].

In general, this biotransformation pathway is highly specific but metabolically low-capacity. The relatively low concentration of PAPS in the cell (about 75 μM , compared to a concentration of UDP-glucuronic acid of about 350 μM) limits the ability to sulfate xenobiotics.

Some xenobiotics are substrates for both sulfotransferases and UDP-glucuronosyltransferases. Substrate concentration, cofactor availability, and certain other conditions influence the choice of the preferred metabolic pathway for a particular chemical compound. For example, the relative content of paracetamol biotransformation products during its metabolism depends on the dose of the administered drug: at low doses, sulfate conjugates predominate in the metabolic products, and as the dose increases, this metabolic pathway becomes saturated and, possibly due to the inhibition of sulfotransferase activity, the relative amount of sulfate conjugates in the metabolic products decreases compared to glucuronic conjugates [16].

Four families of sulfotransferases (SULT1, SULT2, SULT4, and SULT6) and about 40 isoenzymes encoded by 10 genes have been identified in the human body [15]. Based on data on the homology of amino acid sequences of specific isoenzymes and their groups, the sulfotransferase superfamily is divided into a number of subfamilies: 1A, 1B, 1C, 1E, 2A, 2B, etc. (Table 3).

Taking into account substrate specificity, sulfotransferases are divided into the following classes:

- arylsulfotransferases are capable of sulfating many xenobiotics with a phenolic residue;
- alcohol sulfotransferases are capable of metabolizing primary and secondary alcohols, including nonaromatic hydroxysteroids;
- estrogen sulfotransferases are capable of metabolizing aromatic hydroxysteroids;
- tyrosine sulfotransferases are capable of metabolizing tyrosine, methyl esters, and bile acids.

Three types of sulfotransferases have been found in the cytosolic fraction of human hepatocytes: one steroid/bile sulfotransferase, or dehydroepiandrosterone sulfotransferase (DHEA-ST), and two isoenzymes of phenolic sulfotransferase. Phenolic sulfotransferases differ from each other in terms of thermostability — one form of the enzyme is thermostable, while the other is thermolabile. A study of the role of sulfotransferases in the bioactivation of 4-aminobiphenyl showed that N-OH-aminobiphenyl sulfotransferase activity in liver and intestinal cells correlated with the activity of the thermostable form of sulfotransferase, but not with the activity of the thermolabile DHEA-ST form [16].

The isoenzymes of the SULT1 subgroup play the most important role in the sulfation of drugs and their metabolites, with SULT1A1 and SULT1A3 being considered particularly important. The marker substrate for isoenzymes belonging to the SULT1 subgroup is 4-nitrophenol.

Endogenous substrates of SULT1A1 include 17 β -estradiol, while exogenous substrates include drugs such as minoxidil, acetaminophen, morphine,

Table 3. Isoforms of the sulfotransferase family and the drugs they metabolize [15]
Таблица 3. Изоформы семейства сульфотрансфераз и метаболизируемые ими лекарственные средства [15]

Семейство / Family	Ген / Gene	Функция / Function	Хромосомная локализация / Chromosomal localization	Субстраты / Substrates
SULT1	SULT1A1	Сульфирование катехоламинов и других нейротрансмиттеров, фенолов, спиртов и аминов / Sulfation of catecholamines and other neurotransmitters, phenols, alcohols and amines	16p11.2	Парацетамол, миноксидил / Paracetamol, minoxidil
	SULT1A2			Премарин / Premarin
	SULT1A3			Парацетамол, морфин, тапентадол, трамадол / Paracetamol, morphine, tapentadol, tramadol
	SULT1A4			Парацетамол, морфин/ Paracetamol, morphine
	SULT1B1	Конъюгирование тиреоидных гормонов, фенолов, бензиловых спиртов / Conjugation of thyroid hormones, phenols, benzyl alcohols	4q13.3	Тироксин / Thyroxine
	SULT1C2	Метаболизм фенолов / Metabolism of phenols	2q12.3	Парацетамол, морфин / Paracetamol, morphine
	SULT1C3	Метаболизм дофамина, других катехоламинов и биогенных аминов / Metabolism of dopamine, other catecholamines and biogenic amines		Адреналин / Adrenaline
	SULT1C4			Доцетаксел / Docetaxel
	SULT1E1	Метаболизм эстрогенов / Estrogen metabolism	4q13.3	Эстриол / Estriol
SULT2	SULT2A1	Сульфирование стероидов и желчных кислот в печени и надпочечниках / Sulfation of steroids and bile acids in the liver and adrenal glands	19q13.33	Урсосан / Ursosan
	SULT2B1	Конъюгирование дегидроэпиандростерона (ДГЭА) / Conjugation of dehydroepiandrosterone (DHEA)		Циторабин, флударабин, гем-тузумаб, озогамин, идарубицин / Cytarabine, fludarabine, gentuzumab, ozogamicin, idarubicin
SULT4	SULT4A1	Изоформа, специфичная для центральной нервной системы, обеспечивает метаболизм нейротрансмиттеров/ The central nervous system specific isoform mediates the metabolism of neurotransmitters	22q13.31	Адреналин / Adrenaline
SULT6	SULT6B1	Метаболизм тироксина / Thyroxine metabolism	2p22.2	Тироксин / Thyroxine

salicylamide, isadrine, and others. SULT1A3 catalyzes the sulfation reactions of monoamines with phenolic radicals: dopamine, serotonin, norepinephrine [17].

In general, sulfation as a biotransformation pathway is usually effectively accompanied by a decrease in the pharmacological activity and toxicity of xenobiotics. However, in some cases, when foreign compounds are metabolized by enzymatic sulfation, the toxicity of the metabolites exceeds that of the original xenobiotic, since some sulfate conjugates are chemically unstable and degrade, forming strong electrophilic derivatives with high reactivity. Thus, sulfo-conjugation is a necessary step in the activation of many chemical compounds that are procarcinogens (acetylaminofluorene, arylamines, and other procarcinogens). The metabolites of many N-hydroxyarylamines and hydroxamic

acids formed in the sulfo-conjugation reaction also have a mutagenic effect [17].

ENZYMATIC ACETYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

The acetylation reaction, or conjugation with acetic acid, which is considered one of the most evolutionarily ancient reactions of biotransformation of chemical compounds, is catalyzed by the enzyme N-acetyltransferase. In addition to N-acetyltransferase, coenzyme A also participates in the enzymatic acetylation reactions of chemical compounds. In the human body, the intensity of acetylation reactions is influenced by biochemical processes involving pantothenic acid,

pyridoxine, thiamine, lipoic acid, as well as processes associated with the activation of β_2 -adrenoreceptors. Acetylation depends on the functional state of the liver and other organs whose tissue cells contain N-acetyltransferase.

Two isoenzymes of N-acetyltransferase have been identified and isolated — NAT1 and NAT2, which carry out N- and O-acetylation of aromatic and heterocyclic amines and hydrazines, including many carcinogens [24, 57]. NAT1 and NAT2 are similar in structure (depending on the species of the isoenzymes, 79–95% homology of amino acids in the structure of the molecules of these isoenzymes has been found), but they have substrate specificity and different levels of activity in different tissues.

NAT isoenzymes are cytosolic enzymes found in hepatocytes and cells of many other tissues in most mammalian species (except for foxes and dogs, which are incapable of N-acetylation of xenobiotics). NAT1 in adults is found in the liver, gallbladder, GIT, blood cells, placenta, skin, skeletal muscle, mammary gland, prostate, and lungs. NAT2 is mainly present in the liver and small intestine. In addition, NAT1 is found in newborns in the lungs, liver, and adrenal glands, while NAT2 activity only becomes apparent by the end of the first year of life [15].

N-acetylation is the main route of biotransformation of aromatic amines, including drugs containing a hydrazine group ($R-NH-NH_2$). In the N-acetylation reaction, aromatic amines are converted to aromatic amides ($R-NH-COCH_3$) or hydrazides ($R-NH-NH-COCH_3$), respectively [13]. Primary aliphatic amines rarely undergo N-acetylation. An exception is the sequence of biochemical transformations in which cysteine conjugates are formed from glutathione conjugates, from which, in turn, mercapturic acid is formed by N-acetylation in the kidneys.

Many N-acetylated metabolites are less soluble in water than the parent compounds. However, in some cases, such as the metabolism of isoniazid, N-acetylation prior to excretion facilitates the elimination of isoniazid metabolites in the urine (Fig. 1).

More than 20 allelic variants of the NAT2 and NAT1 genes are known, which differ in activity by a factor of ten. Mutations in the N-acetyltransferase loci result in either a slow acetylation phenotype (decreased enzyme activity or stability) or a rapid acetylation phenotype (increased enzyme activity) [2].

Slow acetylators are characterized by an increase in the toxic effect of xenobiotics metabolized with the participation of the enzyme, in particular carcinogenic substances contained in tobacco smoke, exhaust gases, etc., which can contribute to a varying predisposition to malignant neoplasms. Inactivating mutations in the NAT2 gene are associated with susceptibility

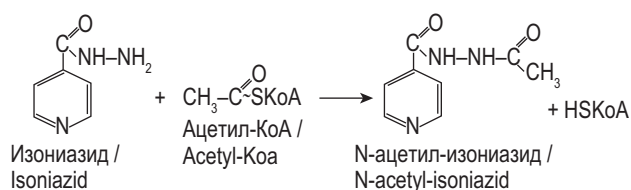


Fig.1. Isoniazid acetylation scheme [15]

Рис. 1. Схема ацетилирования изониазида [15]

to bladder cancer (the risk of developing it increases 3-fold). In rapid acetylators, occupational bladder cancer induced by 2-naphthylamine and benzidine develops significantly less frequently than in slow acetylators [15].

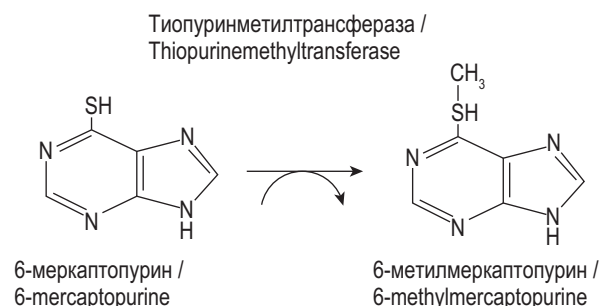
ENZYMATIC METHYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

In the metabolism of xenobiotics, enzymatic methylation reactions are mediated by the activity of methyltransferases. Methyltransferases participate in the methylation of chemical compounds whose molecules contain hydroxyl, sulfhydryl, and amino groups [10, 18]. Thus, phenols, amines, sulfur-containing compounds, thiol poisons (mercury, lead, arsenic, tin, etc.) and some endogenous substances undergo methylation. As a result of methylation, the corresponding O-, N- and S-methyl conjugates are formed. S-adenosylmethionine, which is formed by the interaction of methionine with ATP and is a substrate for about 50 methyltransferases, acts as a methyl group donor.

Compounds containing phenolic groups undergo O-methylation. Under the influence of enzymes (O-methyltransferases), the methyl group attaches to the oxygen atoms of phenolic hydroxyls. In addition to the coenzyme, the presence of magnesium ions or other divalent metals is required for the methylation reaction of phenols. Compounds containing a single phenolic group are not methylated, even in the presence of these enzymes.

During N-methylation, under the influence of N-methyltransferase, a methyl group attaches to the nitrogen atoms of endogenous metabolites or metabolites of foreign compounds. Some foreign compounds containing thiol groups are also methylated in the body. In this case, in the presence of enzymes (S-methyltransferases), the methyl group is transferred to sulfur atoms undergoing biotransformation of metabolites, with the formation of the corresponding S-methyl derivatives of these compounds.

Methylation of xenobiotics, compared to other conjugation reactions, has one feature, which is that the addition of a methyl group does not result in the



Ado-Met — S-аденозил-L-метионин / S-adenosyl-L-methionine

Ado-Hcy — S-аденозил-L-гомоцистеин / S-adenosyl-L-homocysteine

Fig. 2. 6-Mercaptopurine methylation catalysis [15]

Рис. 2. Катализ метилирования 6-меркаптопурина [15]

formation of polar metabolites, but instead eliminates the extremely reactive SH and NH groups of the preceding participants in biotransformation, which neutralizes their high reactivity. Thus, thiopurine methyltransferase catalyzes S-methylation in the metabolism of cytostatics (6-mercaptopurine, azathioprine, and thioguanine) (Fig. 2), preventing the formation of active metabolites — thioguanine nucleotides. Thiopurine methyltransferase deficiency leads to an increase in the concentration of these active metabolites, causing life-threatening myelo- and immunosuppression, which requires a several-fold reduction in the dose of these cytostatics during chemotherapy [34].

Among endogenous substances, the following are metabolized with the participation of the enzyme catechol-O-methyltransferase: adrenaline, noradrenaline, dopamine; phenol-O-methyltransferase — tyrosine, and S-adenosyl-methyltransferase — histamine [15].

ENZYMATIC GLUTATHIONYLATION REACTIONS: FUNCTIONAL SPECIALIZATION OF ENZYMES, INTERMEDIATE PRODUCTS (METABOLITES) OF REACTIONS AND THEIR ACTIVITY

Glutathione S-transferases (GSTs) are involved in glutathionylation enzymatic reactions. These enzymes catalyze the conjugation of xenobiotics with glutathione [5, 12]. Glutathione is a tripeptide consisting of glycine, cysteine, and glutamic acid, which is linked to cysteine via a γ -carboxyl group (Fig. 3). As a result of an enzymatic reaction involving GST, a thioester of the compounds participating in the reaction is formed.

There are three superfamilies of glutathione-S-transferases: cytosolic, mitochondrial, and microsomal. Cytosolic glutathione-S-transferases are divided into 13 classes (alpha, beta, delta, epsilon, zeta, theta, mu, nu, pi, sigma, tau, phi, and omega). Mitochondrial glutathione-S-transferases belong to the kappa class (GSTK). Microsomal glutathione S-transferases are

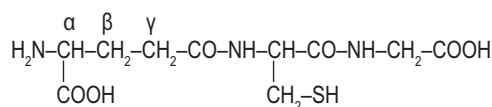


Fig. 3. Structure of glutathione (picture from the Internet)

Рис. 3. Структура глутатиона (рисунок из Интернета)

also known as MAPEG (membrane-associated proteins of eicosanoid and glutathione metabolism). The highest GST activity is observed in the liver, kidneys, brain, heart, lungs, and GIT [7]. 95% of the total enzyme content is localized in the cytoplasm and about 5% in the endoplasmic reticulum of cells.

The substrates for GST are usually hydrophobic compounds containing an electrophilic atom. Substrates for glutathione conjugation can be divided into two groups: 1) sufficiently electrophilic chemical compounds that are capable of direct conjugation with glutathione; 2) chemical compounds that require activation before the conjugation reaction can begin. The second group of compounds includes oxiarenes, alkene epoxides, nitronium ions, carbocation ions, and free radicals [14].

Conformationally, all GSTs have a similar structure and are dimers composed of a combination of two identical or non-identical subunits. GSTs form a superfamily of multifunctional isoenzymes that contribute to detoxification processes. Various mechanisms are involved in the detoxification process, including: 1) non-catalytic binding of certain reactive xenobiotics to glutathione; 2) catalytic inactivation of a wide range of xenobiotics through conjugation with reduced glutathione (GSH); 3) glutathione peroxidase activity, which restores lipid and DNA hydroperoxides [17].

The most important for the metabolism of immunotoxins are GST isoenzymes belonging to the alpha, theta, mu, and pi classes (Table 4), encoded by GST genes, among which the *GSTM1* gene plays an important role in the inactivation of carcinogens. All five genes, *GSTM1*, *GSTM2*, *GSTM3*, *GSTM4*, and *GSTM5* are located on 1p13.3 [15].

GST isoenzymes play an important role in the metabolism of carcinogens, lipids, free radical oxidation products, catecholesterogen metabolism, and detoxification of aflatoxin B1-8,9-epoxide. Human liver GST has catalytic activity toward the reactive metabolite of benz(a)pyrene, benz(a)pyrene-4,5-oxide. In addition to the metabolism of carcinogens and other xenobiotics, GST isoenzymes are involved in the biosynthesis of biologically active molecules, including leukotrienes and prostaglandins, as well as in the binding and biotransformation of bilirubin and steroid hormones (in particular, *in vivo*, GST isoenzymes ensure the transport of these endogenous compounds). GST isoenzymes inhibit the activity of lipid peroxidation (LPO) products and

Table 4. Isoforms of the glutathione-S-transferase family and the substrates they metabolize [15]

Таблица 4. Изоформы семейства глутатион-S-трансфераз и метаболизируемые ими субстраты [15]

Ген / Gene	Функция / Function	Хромосомная локализация / Chromosomal localization	Субстраты / Substrates
<i>GSTA1</i>	Метаболизм эндогенных продуктов окислительного стресса и экзогенных соединений, включая ЛС, канцерогены, иммунотоксиканты и другие токсины / Metabolism of endogenous oxidative stress products and exogenous compounds, including drugs, carcinogens, immunotoxicants and other toxins	6p12.2	Цисплатин, циклофосфамид, доксорубин, ритуксимаб, винкристин, бисульфат, преднизолон / Cisplatin, cyclophosphamide, doxorubicin, rituximab, vincristine, bisulfan, prednisolone
<i>GSTT1</i>		22q11.23	Клозапин, иматиниб, цисплатин, изониазид, этамбутол, пиразинамид, рифампин / Clozapine, imatinib, cisplatin, isoniazid, ethambutol, pyrazinamide, rifampin
<i>GSTM1</i>		1p13.3	Цисплатин, оксалиплатин, блеомицин, доксорубин, винбластин, бисульфат, невирапин, сульфаметоксазол, триметоприм, клозапин, этамбутол, пиразинамид, рифампин / Cisplatin, oxaliplatin, bleomycin, doxorubicin, vinblastine, bisulfan, nevirapine, sulfamethoxazole, trimethoprim, clozapine, ethambutol, pyrazinamide, rifampin
<i>GSTM3</i>			Оланзапин, цисплатин, циклофосфамид / Olanzapine, cisplatin, cyclophosphamide
<i>GSTP1</i>		11q13.2	Циклофосфамид, эпирубин, фторурацил, оксалиплатин, цисплатин, метотрексат, доксорубин, блеомицин, этопозид, изониазид, рифампин / Cyclophosphamide, epirubicin, fluorouracil, oxaliplatin, cisplatin, methotrexate, doxorubicin, bleomycin, etoposide, isoniazid, rifampin

also contribute to the resistance of proteins and nucleic acids to the alkylating effects of the corresponding toxicants [8]. However, the conjugation of phase I biotransformation products with glutathione can also result in the formation of metabolites with higher toxicity than their precursors.

THIRD PHASE OF XENOBIOTICS BIOTRANSFORMATION: MOLECULES-BIOTRANSPORTERS, THEIR FUNCTIONAL SPECIALIZATION

Currently, the third phase of biotransformation is particularly emphasized — the active secretion of xenobiotics and/or their metabolites into urine or bile, which is carried out by proteins belonging to the superfamily of secondary membrane-bound transporters MFS (Major Facilitator Superfamily) [6, 36] and the superfamily of ATP-binding cassette transporters (ABC transporters) [19]. The MFS includes solute carrier family (SLC) proteins (carriers) of the SLC22 [20] and SLC21 (OATP) [21], which carry out the transmembrane transport of “organic electrolytes” — structurally different compounds that have a negative, positive, or both charges (zwitterions) at physiological pH values. These include endogenous substrates of physiological significance, as well as pharmacologically and toxicologically significant xenobiotics [49, 51]. In addition to organic anion transporters (OAT), the SLC22 family includes organic cation transporters (OCT) and carnitine/zwitterion transporters (OCTN).

The ABC transporter superfamily currently comprises approximately 300 eukaryotic proteins that transport a wide variety of compounds [23]. These proteins use ATP energy to move various substrates across the cell membrane. Among ABC transporters, one can distinguish exporters, which transport toxins, drugs, and lipids out of the cell, and importers, which transport nutrients and other molecules into the intracellular space [19, 26, 35].

Phase III transporters are present in many tissues, including the liver, intestines, kidneys, and brain, where they form a barrier against the entry of xenobiotics into the body. These biomolecules play an important role in regulating the absorption, distribution, and excretion of many drugs and toxic xenobiotics, and are also involved in the efflux from cells of newly formed products of the second phase of biotransformation.

ORGANIC ANION TRANSPORTERS: STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic anion transporters play a significant role in the distribution and excretion of an exceptionally wide range of compounds, including endogenous metabolites (hormones, nutrients) and exogenous organic anions. Large hydrophobic organic anions, including a wide range of drugs, serve as OAT substrates. Transmembrane transport mediated by OAT occurs in numerous organs, including the kidneys, liver, brain, retina, adrenal glands, pancreas, intestines, and placenta [55].

The localization, substrate specificity, and ligands of the main OATs are presented in Table 5.

All members of the OAT family are characterized by a similar structure, a high level of genetic sequence conservation, and transport a wide range of weakly acidic drugs, such as loop and thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, beta-lactam antibiotics, sulfonamides, and antivirals.

The OAT polypeptide chain, consisting of 536–556 amino acid residues, penetrates the cell membrane 12 times and forms a pore. Characteristic of this protein is the intracellular localization of the N- and C-terminal regions of the molecule and two large connecting loops between helices 1–2 and helices 6–7. Two domains containing ATP binding sites are located in the intracellular space of the cell.

The primary function of OAT is to transport one organic anion into the cell in exchange for another organic anion out of the cell. Although most OATs are

Na-independent anion exchangers [49], their function is indirectly linked to the Na⁺ gradient through tertiary active transport, which involves Na,K-ATPase and Na-dependent dicarboxylic acid transport [53]. The uptake of organic anions into the cell occurs in exchange for intracellular α -ketoglutarate, which is a metabolite of the Krebs cycle and the preferred physiological counterion exiting the cell. Na-dependent α -ketoglutarate transport is maintained by the Na⁺ gradient created by Na,K-ATPase.

With broad substrate specificity, OATs can interact with a wide variety of compounds and transport not only small amphiphilic organic anions and uncharged molecules, but also xenobiotics and their metabolites, which are ionized during metabolism.

OATs function in interaction with enzymes of the first and second phases of biotransformation, actively participating in the distribution and elimination of metabolites [58]. OAT-3 is better adapted to the transfer of glucuronidated and sulfated xenobiotics than unmodified

Table 5. Transporters of organic anions of the organic anion transporters (OAT) subfamily [48]

Таблица 5. Транспортеры органических анионов подсемейства транспортеров органических анионов (OAT) [48]

Транспортер / Transporter	Ген / Gene	Локализация / localization	Субстраты лекарственных средств / Substrates-therapeutic agents
OAT-1	SLC22A6	Почки, сосудистое сплетение мозга, плацента / Kidneys, choroid plexus of the brain, placenta	Антигипертензивные средства, тиазидные диуретики, статины, антибиотики, противовирусные средства, нестероидные противовоспалительные препараты, соединения ртути, низкомолекулярные ксенобиотики, антагонисты гистаминовых рецепторов / Antihypertensives, thiazide diuretics, statins, antibiotics, antivirals, nonsteroidal anti-inflammatory drugs, mercury compounds, low molecular weight xenobiotics, histamine receptor antagonists
OAT-2	SLC22A7	Печень, почки / Liver, kidneys	Антибиотики, диуретики, антагонисты гистаминовых рецепторов, противовирусные средства, нестероидные противовоспалительные препараты, противоопухолевые средства / Antibiotics, diuretics, histamine receptor antagonists, antiviral agents, nonsteroidal anti-inflammatory drugs, antineoplastic agents
OAT-3	SLC22A8	Почки, эндотелий гематоэнцефалического барьера, сосудистое сплетение мозга, сетчатка глаза, семенники / Kidneys, endothelium of the blood-brain barrier, choroid plexus of the brain, retina, testes	Диуретики, антибиотики, противовирусные средства, антагонисты гистаминовых рецепторов, нестероидные противовоспалительные средства, низкомолекулярные ксенобиотики / Diuretics, antibiotics, antivirals, histamine receptor antagonists, nonsteroidal anti-inflammatory drugs, low molecular weight xenobiotics
OAT-4	SLC22A11	Почки, плацента, надпочечники / Kidneys, placenta, adrenal glands	Диуретики, антибиотики, нестероидные противовоспалительные препараты / Diuretics, antibiotics, nonsteroidal anti-inflammatory drugs
OAT-6	SLC22A20	Назальная слизистая, семенники, печень / Nasal mucosa, testes, liver	Эстрона сульфат, одоранты / Estrone sulfate, odorants
OAT-7	SLC22A9	Печень / Liver	Эстрона сульфат, дегидроэпиандростерона сульфат / Estrone sulfate, dehydroepiandrosterone sulfate
OAT-10	SLC22A13	Почки, мозг, сердце, тонкий и толстый кишечник / Kidneys, brain, heart, small and large intestines	Никотин, ураты / Nicotine, urates

organic anions [48]. Thus, the interaction between OATs and enzymes of the first and second phases of biotransformation is aimed at the inactivation of xenobiotics, the immunotoxicity of which may increase during their metabolism. This interaction also ensures the maintenance of homeostasis in terms of the formation and inactivation of signaling molecules involved in long-distance communication between various tissues and organs.

POLYPEPTIDE TRANSPORTERS OF ORGANIC ANIONS: STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic anion transporting polypeptides (OATPs) are members of the Na-independent transport system that transport numerous endogenous and exogenous amphiphilic organic anions with molecular masses greater than 350 Da across plasma membranes at physiological pH values [50]. These transporters transport bilirubin and various drugs (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, antihistamines, and antitumor agents) [39]. In addition, they are key players in the

redistribution and elimination of various xenobiotics, including immunotoxicants, from cells [52].

OATPs contain 643–722 amino acids. Depending on the degree of glycosylation, the molecular mass varies from 65 to 120 kDa [38]. The transport channel is formed by a polypeptide chain that spans the cytoplasmic membrane 12 times and has six extracellular loops [56]. Glycosylation occurs actively on loops 2 and 5, where carbohydrate attachment sites are located [59]. Within the site, a pore-like space generates a positive charge due to the exposure of positively charged amino acids to the interior, resulting in the binding and transport of negatively charged molecules, which represent the bulk of OATP substrates, into the cell.

OATP is expressed in various epithelial cells (Table 6) [37]. In humans, OATP is divided into six families (OATP1–OATP6), which are further grouped into subfamilies based on the location of the gene encoding the protein. The mechanism of transport of various molecules by OATP has not yet been fully elucidated [37]. It is known that many OATPs are antiporters, i.e., they simultaneously transport anions across the membrane in opposite directions. In the proposed models,

Table 6. Human organic anion transporter proteins (OATP) [39]

Таблица 6. Белки-транспортёры органических анионов (OATP) человека [39]

Семейство / Family	Подсемейство / Subfamily	Локализация / localization	Переносимые субстраты / Transferable substrates
OATP-1	OATP1A2	Мозг, почки, печень, легкие, семенники, плацента / Brain, kidneys, liver, lungs, testes, placenta	Холаты, органические анионы / Cholates, organic anions
	OATP1B1	Печень / Liver	Холаты, билирубин / Cholates, bilirubin
	OATP1B3	Печень, злокачественные опухоли / Liver, malignant tumors	Холаты, билирубин, глутатион, простагландины, лейкотриены, трийодтиронин, тироксин / Cholates, bilirubin, glutathione, prostaglandins, leukotrienes, triiodothyronine, thyroxine
	OATP1C1	Глиальные клетки гипоталамуса, сосудистые сплетения гематоэнцефалического барьера, клетки Лейдига / Hypothalamic glial cells, choroid plexuses of the blood- brain barrier, Leydig cells	Холаты, трийодтиронин, тироксин, эстрон-3-сульфат / Cholates, triiodothyronine, thyroxine, estrone-3-sulfate
OATP-2	OATP2A1	Во всех тканях / In numerous tissues	Простагландины, тромбоксан / Prostaglandins, thromboxane
	OATP2B1	тРНК найдена во многих органах / tRNA is found in many organs	Бромсульфаталеин / bromosulphthalein
OATP-3	OATP3A1	Во всех тканях / In numerous tissues	Эстрон-3-сульфат, простагландины / Estrone-3-sulfate, prostaglandins
OATP-4	OATP4A1	Во всех тканях / In numerous tissues	Таурохолат, трийодтиронин / taurocholate, triiodothyronine
	OATP4C1	Локализация неизвестна / Unknown localization	Трийодтиронин / triiodothyronine
OATP-5	OATP5A1	Эпителий протоков молочной железы / Epithelium of the mammary gland ducts	Нет данных / No data
OATP-6	OATP6A1	Семенники, мозг, плацента / Testicles, brain, placenta	Нет данных / No data

the largest pore diameter is observed on the cytoplasmic side. Conformational changes in the transporter molecule can cause the pore to open toward the extracellular space. Intracellular ions can act as energy sources for transporting other anions into the cell. It is assumed that one of these intracellular substrates is reduced glutathione (GSH), which can act as an energy donor when OATPs perform their functions of transporting substances into the cell [43]. The intracellular concentration of GSH, which is 1000 times higher than its content outside the cell, and its negative charge at physiological pH values can provide energy to OATP1 when performing its transport functions [27]. Moreover, it is the intracellular level of GSH, and not its transmembrane gradient, that plays a decisive role in implementing the OATP transport function [44].

OATPs play an active role in the functioning of the xenobiotic biotransformation system. Due to their expression in most tissues, OATPs play a major role in the transport of many endo- and exogenous compounds into virtually all cell types and associated tissues and organs [52].

A number of drug-drug interactions (DDIs) discovered in recent years have demonstrated the impossibility of explaining the biotransformation of drugs solely by the activity of phase I and phase II enzymes of xenobiotic metabolism. It has been shown that the interaction between cytochromes P450 (CYP) and transporters plays a key role in these processes [60], which can be mediated through altered metabolic pathways due to simultaneous changes in enzyme and transporter activity. Drugs targeting phase I and phase II enzymes can often be substrates or inhibitors of transporters. When using OATP inhibitors, plasma drug concentrations may increase and the risk of developing side effects such as hepatotoxicity, nephrotoxicity, and immunotoxicity may increase [47]. When both inhibitors are used concomitantly, the CYP-OATP interaction may result in a synergistic rather than additive effect. This interaction may be determined through co-regulation of protein expression. The expression of both components is believed to be regulated by a family of transcription factors known as nuclear receptors, such as PXR (pregnane X receptor), CAR (constitutive androstane receptor), FXR (farnesoid X receptor), and LXR (liver X receptor).

ORGANIC CATION TRANSPORT PROTEINS (OCAT) AND CARNITINE/ZWITTERION TRANSPORT PROTEINS (OCTN): STRUCTURE, TISSUE LOCALIZATION, AND MECHANISM OF TRANSPORT FUNCTIONS

Organic cation transporters (OCT) and carnitine/zwitterion transporters (OCTN) participate in the trans-

port of organic cations across the cell membrane exclusively in the direction of their electrochemical gradient. Their molecular diversity is significantly lower than that of other transporters: three organic cation transporters are known — OCT1, OCT2, OCT3 — and three carnitine/zwitterion transporters — OCTN1, OCTN2, OCT6 [49, 61].

OCT and OCTN are present in many tissues, which indicates their active participation in tissue and organ metabolism (Table 7). They are particularly abundant in the liver, kidneys, brain, and intestines, where they participate in the absorption, distribution, and excretion of xenobiotics and endogenous metabolites. In the proximal renal tubules, OCT transporters are involved in the active secretion of hydrophilic endogenous and exogenous compounds into the urine.

They are structurally similar to other proteins of the MFS superfamily and consist of 543–557 amino acids forming 12 transmembrane helices (domains). Three N-glycosylation sites are located on a large extracellular loop between the first and second transmembrane domains, ensuring accurate folding and positioning in the cell membrane [29]. Phosphorylation sites are located on a large intracellular loop connecting the 6th and 7th helices. Protein kinases A (PKA), C (PKC), G (PKG) and calcium/calmodulin-dependent protein kinase II (CaMKII) are involved in phosphorylation reactions [31]. The N- and C-terminal halves of the transporter form a cleft, and binding to ligands and substrate transport presumably occurs through interaction with amino acid residues facing the interior of the cleft [22].

The main substrates of these transporters are organic compounds of endogenous and exogenous origin, structurally unrelated to each other and carrying a positive charge at physiological pH. For transmembrane transport of organic cations, transporters use the negative charge existing on the inner surface of cell membranes [40]. Passive diffusion of cations occurs along the electrochemical gradient, causing the corresponding substrates to accumulate inside the cell in concentrations significantly higher (up to 10 times) than outside [32]. The higher the degree of ionisation of the substrates, the higher their affinity for the transporter and the rate of their transport as the pH decreases [28].

ATP-BINDING CASSETTE TRANSPORTERS OF THE ABC FAMILY: STRUCTURE, TISSUE LOCALISATION, MECHANISM OF TRANSPORT FUNCTIONS

ATP-binding cassette transporters (ABC) are the largest class of membrane-bound proteins that transport metabolic products across both the plasma membrane and the intracellular membranes of various

Table 7. Tissue distribution and substrate specificity of OCT/OCTN transporters [41]**Таблица 7.** Тканевое распределение и субстратная специфичность транспортеров OCT/OCTN [41]

Транспортер / Transporter	Тканевое распределение / Tissue distribution	Основные эндогенные субстраты / Main endogenous substrates	Основные экзогенные субстраты / Main exogenous substrates
OCT-1	Печень, почки, тонкая кишка, легкие, скелетная мускулатура, головной мозг, жировая ткань, иммунные клетки / Liver, small intestine, kidney, lung, skeletal muscle, brain, adipose tissue, immune cells	Путресцин, гистидил-пролил-дикетопиперазин, салсолин-нол, агматин / Putrescine, hys-pro-diketopiperazine, salsolinol, agmatine	Метформин, ацикловир, пентамидин, фураимидин, оксиплатин, афлатоксин В1, этидиумбромид и др. / Metformin, acyclovir, pentamidine, furamide, oxaliplatin, aflatoxin B1, ethidiumbromide, etc.
OCT-2	Почки, тонкая кишка, легкие, плацента, тимус, головной мозг, клетки внутреннего уха / Kidney, small intestine, lung, placenta, thymus, brain, inner ear cells	Ацетилхолин, дофамин, эpineфрин, норэpineфрин, серотонин, гистамин, путресцин, холин, салсолин-нол / Acetylcholine, dopamine, epinephrine, norepinephrine, serotonin, histamine, putrescine, choline, salsolinol	Амантин, цисплатин, афлатоксин В1, этидиумбромид, паракват и др. / Amantadine, cisplatin, aflatoxin B1, ethidiumbromide, paraquat, etc.
OCT-3	Сердце, скелетная мускулатура, головной мозг, тонкая кишка, печень, легкие, почки, мочевой пузырь, молочная железа, кровеносные сосуды кожи / Heart, skeletal muscle, brain, small intestine, liver, lung, kidney, urinary bladder, mammary gland, skin blood vessels	Эpineфрин, норэpineфрин, гистамин, агматин, гистидил-пролил-дикетопиперазин, салсолин-нол / Epinephrine, norepinephrine, histamine, agmatine, cyclo(His-Pro), salsolinol	Лидокаин, метформин, оксиплатин, квинидин, этилэфрин и др. / Lidocaine, metformin, oxaliplatin, quinidine, etilefrine, etc.
OCTN-1	Почки, кишечник, брыжейка, сердце, скелетная мускулатура, головной мозг, молочная железа, тимус, простата, семенники, глаз, сперма, иммунные клетки / Kidney, intestine, mesentery, heart, skeletal muscle, brain, mammary gland, thymus, prostate, testis, eye, sperm, immune cells	Ацетилхолин, эрготионеин, глицил-бетаин, L-карнитин / acetylcholine, ergothioneine, glycinebetaine, L-carnitine	Квинидин, верапамил, ипратропиум, митоксантрон, доксорубин, бетоницин и др. / Quinidine, verapamil, ipratropium, mitoxantrone, doxorubicine, betonicine, etc.
OCTN-2	Скелетная мускулатура, почки, простата, легкие, печень, поджелудочная железа, сердце, тонкая кишка, надпочечники, щитовидная железа / Skeletal muscle, kidney, prostate, lung, pancreas, heart, small intestine, adrenal gland, thyroid gland, liver	L-карнитин, холин / L-carnitine, choline	Милдронат, цефалоридин, эметин, верапамил, шпиронолактон, оксиплатин и др. / Mildronate, cephaloridine, emetine, verapamil, spironolactone, oxaliplatin, etc.
OCT-6	Семенники (клетки Сертоли и семенного протока), почки, лейкоциты, костный мозг / Testis (Sertoli cells and epididymal duct cells), kidney, leukocytes, bone marrow	L-карнитин, спермидин / L-carnitine, spermidine	Доксорубин, блеомицин А5 / Doxorubicin, bleomycin A5

organelles: the endoplasmic reticulum, peroxisomes, and mitochondria [33]. These proteins are named for their use of ATP as an energy source to transport various molecules. It has been found that ABC transporters are involved in many pathological processes: in the development of multiple drug resistance, oncogenesis, autoimmune reactions, and degenerative protein metabolism pathology [19, 25].

ABC transporters differ in amino acid sequence, structural and domain structure and are divided into 7 subfamilies: ABCA, ABCB, ABCC, ABCD, ABCE, ABCF and ABCG. All ABC transporters can also be divided into complete transporters, which have four domains (2 transmembrane domains (TMD1, TMD2) and 2 nucleotide-binding domains (NBD1, NBD2)) and

incomplete transporters, which have one TMD and one NBD in their structure [3, 26]. Incomplete transporters are located in the intracellular membranes of organelles and usually assemble into hetero- or homodimers. TMDs penetrate the membrane and have ligand binding sites on their intracellular side. NBD domains, located in the cytoplasm, have binding sites for two ATP molecules and possess ATPase activity. The energy of ATP hydrolysis is used to transport the substrate [45].

ABC transporters are located in virtually all tissues of internal organs, as well as in tumour cells. The most important for the transport of drugs, xenobiotics, including immunotropic substances, are representatives of the ABCB, ABCC and ABCG subfamilies

Table 8. Tissue distribution and substrate specificity of human ABC transporters [54]**Таблица 8.** Тканевое распределение и субстратная специфичность ABC-транспортеры человека [54]

Транспортер / Transporter	Тканевое распределение / Tissue distribution	Основные субстраты / Main substrates
ABCB1 (Pgp)	Гематоэнцефалический барьер, печень, кишечник, почки, плацента, стволовые клетки / Blood-brain barrier, liver, intestine, kidney, placenta, stem cells	Противоопухолевые препараты (доксорубицин, винбластин, этопозид, паклитаксел, метотрексат), анальгетики (морфин), ингибиторы протеазы ВИЧ (ампренавир, индинавир), цитокины (IL-2, IL-4), антидиарейные препараты (лоперамид), антигельминтики (ивермектин, абамектин), противорвотные препараты (домперидон, ондасетрон), сердечные гликозиды (дигоксин), антидепрессанты (амитриптилин, пароксетин), антибиотики (эритромицин, тетрациклины), средства против подагры (колхицин, гистамин), антагонисты H ₂ -рецептора (циметидин), блокаторы кальциевых каналов (верапамил), противозипелитические препараты (карбамазепин, ламотригин, фенобарбитал, габапентин) / Anticancer drugs (doxorubicine, vinblastine, etoposide, paclitaxel, methotrexate), analgesics (morphine), HIV protease inhibitors (amprenavir, indinavir), cytokines (IL-2, IL-4), anti-diarrheal agents (loperamide), anthelmintic agents (ivermectin, abamectin), antiemetics (domperidone, ondansetron), cardiac glycosides (digoxin), antidepressants (amitryptiline, paroxetine), antibiotics (erythromycin, tetracyclines), anti-gout agents (colchicines, histamine), H ₂ -receptor antagonists (cimetidine), calcium channel blocker (verapamil), antiepileptic drugs (carbamazepine, lamotrigine, phenobarbital, gabapentin)
ABCC1 (MRP1)	Легкие, семенники, почки, скелетная и сердечная мускулатура, плацента / Lung, testes, kidney, skeletal and cardiac muscle, placenta	Противоопухолевые препараты: этопозид, тенипозид, винкристин, лейкотриены C4 (LTC4), D4, E4, различные глутатион-, глюкуронид- и сульфат-конъюгаты, а также неконъюгированные соединения (флуоресцеин) / Anticancer drugs: etoposide, teniposide, vincristine, leukotriene C4 (LTC4), D4, E4, various glutathione, glucuronide, and sulfate conjugates, but also unconjugated compounds (fluorescein)
ABCC2 (MRP2)	Гематоэнцефалический барьер, печень, кишечник, почки, плацента, легкие / Blood-brain barrier, liver, intestine, kidney, placenta, lung	Противоопухолевые препараты: этопозид, тенипозид, винкристин, лейкотриены C4 (LTC4), D4, E4, различные глутатион-, глюкуронид- и сульфат-конъюгаты, а также неконъюгированные соединения (флуоресцеин) / Anticancer drugs: etoposide, teniposide, vincristine, leukotriene C4 (LTC4), D4, E4, various glutathione, glucuronide, and sulfate conjugates, but also unconjugated compounds (fluorescein)
ABCC3 (MRP3)	Надпочечники, кишечник, поджелудочная железа, желчный пузырь, плацента, печень, почки, простата / Adrenal gland, intestine, pancreas, gallbladder, placenta, liver, kidney, prostate	Транспортер органических анионов со значительным сходством субстратной специфичности с MRP1 и MRP2 / Organic anion transporter with considerable overlap in drug substrates with MRP1 and MRP2
ABCC4 (MRP4)	Яичники, семенники, почки, легкие, простата / Ovary, testes, kidney, lung, prostate	Противоопухолевые препараты, такие как метотрексат, 6-меркаптопурин, тиогуанин / Anticancer drugs such as methotrexate, 6-mercaptopurine, thioguanine
ABCC5 (MRP5)	Печень, семенники, скелетная и сердечная мускулатура, мозг / Liver, testes, skeletal and cardiac muscle, brain	BQ-123 (анионный циклопентапептид, антагонист рецептора эндотелина) / BQ-123 (an anionic cyclopentapeptide and endothelin receptor antagonist)
ABCG2/BCRP	Гематоэнцефалический барьер, плацента, печень, кишечник, молочная железа, стволовые клетки / Blood-brain barrier, placenta, liver, intestine, breast, stem cells	Противоопухолевые препараты, значительное субстратное перекрытие с Pgp, MRP1 и MRP2, антрациклины, митоксантрон, бисантрон, празолин / Several anticancer drugs; considerable substrate overlap with Pgp, MRP1, and MRP2, anthracyclines, mitoxantrone, bisantrene, prazosin

(Table 8). In addition to the drugs themselves, these proteins transport their sulphated, glutathionylated and glucuronidated metabolites. The most studied representative of the ABC family in humans is the ABCB1 transporter (P-glycoprotein, Pgp, MDR1). This transporter is highly expressed in cells of the

blood-brain barrier, liver, intestine, kidneys, placenta, and stem cells [19].

P-glycoprotein works as a transmembrane pump that removes drugs and other xenobiotics from cells, increasing the excretion of drugs or toxins in bile and urine. The apical (or luminal) location of P-glycoprotein

in the epithelium of the intestinal mucosa leads to a decrease in drug absorption from the gastrointestinal tract. When the functioning of this mechanism of transport of xenobiotic metabolites, which is provided by P-glycoprotein, is disrupted under conditions of severe oxidative stress, other metabolite elimination systems become inadequate or insufficient. These metabolites begin to accumulate in tissue structures, where they exert their toxic effects.

The development of multidrug resistance (MDR) is associated with high activity of the ABCG2 transporter, which is involved in the transport of conjugated drugs and toxins into bile and urine [42]. By removing anticancer drugs from cells and reducing their intracellular concentration, ABC transporters play a key role in the development of tumour MDR, which negatively affects the effectiveness of chemotherapy.

Breast cancer resistance protein (BCRP, ABCG2) is a semi-transporter and functions as a homodimer, actively removing anthracyclines, DNA topoisomerase I inhibitors, and tyrosine kinases from tumour cells [46].

CONCLUSION

Phase II biotransformation reactions are traditionally regarded as detoxification processes. However, there are examples of chemical compounds that, in second-phase metabolism reactions, are converted into active electrophilic metabolites capable of covalent interactions with macromolecules in the body, including proteins, by binding to nucleophilic sites of these macromolecules. As a result of such interactions, reactive metabolites modify the antigenic specificity of these macromolecules as autoantigens and induce autosensitisation of the body, which can contribute to the development of allergic and autoimmune diseases, as well as increase the procarcinogenic activity of chemical carcinogens.

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Phase III metabolism transporters are an integral part of the xenobiotic biotransformation system and play an important role in its functioning through close interaction with phase I and II enzymes. This role consists not only in the conversion of various types of endogenous metabolites, drugs and toxins, but also in the implementation of the interconnection between metabolic processes and signal transmission. The importance of studying transporter proteins is particularly relevant at present, as it is linked to the development of methods and approaches for evaluating the effectiveness and consequences of the use of newly created drugs.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Posterior urethral valves in children. Literature review

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ABSTRACT

The posterior urethral valve is the most common cause of infravesical obstruction in newborn boys with a prevalence of about 1 in 3800. The etiology is multifactorial, associated with impaired embryogenesis in the 4th week of pregnancy with abnormal fusion of the mesonephral ducts with the cloaca. The pathogenesis includes mechanical obstruction of the urethra, leading to increased intravesical pressure, secondary changes in the bladder (detrusor hypertrophy, trabecularity), vesicoureteral reflux (up to 50% of cases) and progressive kidney damage. Prenatal ultrasound can diagnose up to 47% of cases based on the following symptoms: bilateral ureterohydronephrosis, megacystis, keyhole symptom, oligo-/anhydramnion. The basis of treatment is early endoscopic valve ablation in the first months of life and the initiation of drug therapy with M-holinoblockers (oxybutynin), which improves urodynamics and prognosis. If primary ablation is not possible, temporary urine withdrawal (catheterization, cystostomy) is used. Long-term complications include the formation of a "valvular bladder" with neurogenic dysfunction, persistent vesicoureteral reflux, chronic kidney disease (develops in 30–50% of patients), which requires constant dynamic monitoring, urodynamic control, and in some cases, augmentation cytoplasty or renal replacement therapy. Prenatal diagnosis and early minimally invasive intervention remain key to improving outcomes.

Keywords: posterior urethral valve, renal failure, valvular bladder, vesicoureteral reflux, valve ablation, children

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Клапан задней уретры у детей. Обзор литературы

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РЕЗЮМЕ

Клапан задней уретры — наиболее частая причина инфравезикальной обструкции у новорожденных мальчиков с распространенностью около 1:3800. Этиология мультифакториальна, связана с нарушением эмбриогенеза на 4-й неделе беременности при аномальном слиянии мезонефральных протоков с клоакой. Патогенез включает механическую обструкцию уретры, приводящую к повышению внутрипузырного давления, вторичным изменениям мочевого пузыря (гипертрофия детрузора, трабекулярность), пузырно-мочеточниковому рефлюксу (до 50% случаев) и прогрессирующему поражению почек. Пренатальное ультразвуковое исследование позволяет диагностировать до 47% случаев по признакам: двусторонний уретерогидронефроз, мегацистис, симптом «замочной скважины», олиго-/ангидрамнион. Основой лечения является ранняя эндоскопическая абляция клапана в первые месяцы жизни и начало медикаментозной терапии М-холиноблокаторами (оксибутинин), что улучшает уродинамику и прогноз. При невозможности первичной абляции применяется временное отведение мочи (катетеризация, цистостомия). Долгосрочные осложнения включают формирование «клапанного мочевого пузыря» с нейрогенной дисфункцией, персистирующий пузырно-мочеточниковый рефлюкс, хроническую болезнь почек (развивается у 30–50% пациентов), что требует постоянного динамического наблюдения, уродинамического контроля, а в части случаев — аугментационной цистопластики или заместительной почечной терапии. Пренатальная диагностика и раннее малоинвазивное вмешательство остаются ключевыми для улучшения исходов.

Ключевые слова: клапан задней уретры, почечная недостаточность, клапанный мочевой пузырь, пузырно-мочеточниковый рефлюкс, абляция клапана, дети

Как цитировать

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BACKGROUND

The research of infravesical obstruction caused by a urethral valve spans more than 300 years. A congenital posterior urethral valve was first described by Giovanni Battista Morgagni in 1717 [39]. The earliest known mention of posterior urethral valves as valve-like folds of the mucous membrane in autopsy findings dates back to 1802. However, the researcher did not conclude that these findings had any clinical significance [35]. Subsequently, there were isolated reports describing these structures as a result of autopsies [2]. In 1870, research findings on semilunar valves of the urethra in children were published, and in 1875, a comprehensive description of the valves as a pathological phenomenon was provided, along with a hypothesis regarding their origin [48]. The first cases of ante-mortem diagnosis of posterior urethral valves and their successful treatment were described in 1913. A classification of posterior urethral valves in children, which remains relevant to this day, was presented shortly thereafter [54].

ETIOLOGY, EMBRYOLOGY, CLASSIFICATION, AND EPIDEMIOLOGY

The exact cause of posterior urethral valves is unknown, but it is likely a multifactorial embryopathy. Familial inheritance is rare, but such cases have been described [12]. During embryogenesis, the most caudal end of the Wolffian duct opens into the primitive cloaca at the site of the future seminal hillock in the posterior urethra. In healthy males, the residual structures are the posterior urethral folds, known as *plicae colliculi* [41]. Histological examination shows that the posterior urethral valve (PUV) forms around the 4th week of gestation, when the Wolffian duct fuses with the developing cloaca. If the confluence of the mesonephric ducts into the cloaca is abnormal or occurs too distally, normal duct migration is disrupted, and they merge in front of the seminal tubercle, leading to abnormal ridges or folds, which are believed to be the source of 95% of PUVs [24]. This type is called Type I PUV. Although Hugh Young described Type II PUV, most pediatric urologists believe that these are not obstructive valves but simply hypertrophy of the mucosal folds of the bladder neck. Type III valves account for the remaining 5% and consist of a ring-shaped membrane located distally to the seminal tubercle, with a central perforation. Type III valves result from incomplete resolution of the urogenital membrane [24].

H. Young's classification of posterior urethral valves [54] includes three types.

1. Type I valves. These are found in 90–95% of patients as sail-like folds originating from the urethral crest (*crista urethralis urethrae masculinae* — a longitudinal fold on the posterior wall of the urethra extending from the bladder neck through the prostatic urethra),

extend distally, curving around the seminal tubercle on both sides, and merge in front of the membranous portion of the urethra.

2. Type II valves. These are natural folds of the mucous membrane extending from the seminal tubercle to the bladder neck. They are rarely detected. Since they almost never affect the passage of urine through the urethra, they are considered a variant of the anatomical norm.

3. Type III valves. Diagnosed in 5–10% of cases. They consist of a solid diaphragm or a ring-shaped membrane with a central opening, located at the level of the seminal tubercle or slightly distally along the urethra. They can significantly restrict urination [54].

Currently, it is debatable whether Young's classification is appropriate, since in some cases the valves detected during cystoscopy cannot be classified under any of Young's valve types [3].

In congenital urinary tract obstruction (CUTO), there are urinary system lesions of varying severity, which depend on the degree of obstruction. The pathological process is not limited to transient infravesical obstruction. Congenital obstruction of the urinary tract at a critical stage of organogenesis can have a significant impact on kidney, ureter, and bladder function [11].

Appearance of the posterior urethral valve is the primary pathology causing mechanical obstruction of the urethra, leading to subsequent secondary changes. The severity of these changes depends on the degree and timing of the primary obstruction [32].

From the 20th week of gestation, the fetal kidneys produce 90% of the amniotic fluid. An adequate volume of amniotic fluid is vital for lung and skeletal development [49]. Severe oligohydramnios or anhydramnios, caused by decreased urine output, leads to a reduced uterine cavity. This results in compression of the fetus, which impedes normal growth and expansion of the fetal chest, in turn causing lung hypoplasia and soft tissue deformities [19, 32]. The typical fetal phenotype associated with oligohydramnios/anhydramnios includes low-set ears, wide-set eyes, micrognathia, limb contractures, and clubfoot (Potter's sequence) [16]. An adequate volume of amniotic fluid (produced by the kidneys) is necessary for complete and proper branching of the bronchial tree and the formation of alveoli. Bladder distension and urinary ascites increase the fetal abdominal volume and disrupt the development of the abdominal wall muscles, leading to a wrinkled abdomen. Spontaneous decompression of the upper urinary tract can lead to urinary ascites, paraneural, or perineal urinoma [5, 32]. Severe oligohydramnios, azotemia, and severe pulmonary hypoplasia can result in fetal death.

Obstruction of the posterior urethra leads to increased intravesical pressure, progressive thickening

of the muscles (hypertrophy and hyperplasia), trabeculation, the formation of diverticula, and, in severe cases, paravesical or paraurethral urinoma. Some authors believe that a large bladder diverticulum provides some degree of protection for the upper urinary tract due to a pressure-relief mechanism, which is associated with a good prognosis [8, 41]. However, there are publications reporting that a bladder diverticulum or urinoma did not subsequently result in incidence of end-stage renal failure compared to a group in which these complications did not occur [27]. A bladder with pronounced trabeculation exhibits an increase in collagen and connective tissue elements. This leads to the following changes: high intravesical pressure, increased residual urine volume, elevated pressure during micturition, and bladder dysfunction even after valve ablation [32].

Ureteral dilation may occur in PUV due to vesico-ureteral reflux (VUR). It is present in 50% of patients with PUV. VUR may occur either primarily due to pathology of the ureterovesical segment or secondarily due to high intravesical pressure [41]. A significant portion of vesicoureteral reflux resolves after the obstruction is removed [17].

Renal pathology includes hydronephrosis and progressive renal damage. Hydronephrosis is caused by: 1) vesicoureteral reflux; 2) obstruction — high intravesical pressure transmitted to the ureter and kidney via hydrostatic pressure; 3) abnormal development of the ureteric bud, leading to renal dysplasia and dilatation of the collecting system.

Renal damage is caused by the following two factors.

- 1) Renal dysplasia is likely caused by damage during the early fetal period or abnormalities in embryogenesis. It manifests as microcysts, which are found primarily in the peripheral cortical zone. Histological findings include disorganization of the renal parenchyma, the presence of embryonic tubules and cysts, as well as the presence of mesenchymal connective tissue. These changes are irreversible and cause renal failure.
- 2) Obstructive uropathy is kidney damage caused by infravesical obstruction, leading to dysfunction of both the glomeruli and tubules, with a decrease in glomerular filtration rate, reduced kidney function, fibrosis and sclerosis of the renal parenchyma, and tubular damage, which causes impaired urine concentration and acidification. Consequently, diuresis increases, sodium loss rises, and electrolyte imbalances occur. These changes are potentially reversible [22].

The incidence of PUV is approximately 1 in 3,800 live-born boys. PUV is the most common cause of infravesical obstruction in newborn boys [13].

DIAGNOSIS

Early diagnosis of PUV has become possible with advances in prenatal ultrasound (US) of the fetus. Currently, up to 46.9% of PUV cases are detected during prenatal screening [37]. Suspected PUV before the 24th week of pregnancy is associated with an increased risk of perinatal mortality and renal impairment [30]. Key ultrasound findings associated PUV include bilateral hydronephrosis, megacystis with wall thickening (>3 mm), and posterior urethral dilation (keyhole sign) [9, 15]. Oligo/anhydramnios may be an important prognostic sign [14].

Postnatal diagnosis involves ultrasound, voiding cystourethrography, and videocystoscopy, which remains the “gold standard” for confirming the diagnosis.

TREATMENT

Prenatal treatment. Based on pathophysiological considerations, fetal surgery and the vesicoamniotic shunting technique were once viewed with great promise. However, a randomized international multicenter study showed inconclusive results regarding actual long-term improvement in renal function in patients who received this treatment. Moreover, the complication rate ranged from 21% to 59% [40]. Two additional intrauterine techniques have recently been proposed: valve ablation via cystoscopy and vesicostomy via open fetal surgery. However, both techniques are associated with high maternal and perinatal morbidity [31, 51]. Maternal complications include premature rupture of the amniotic membranes, while fetal complications include migration of the vesicoamniotic shunt, eversion of the intestinal loop and omentum into the amniotic cavity, urinoma, and intestinal perforation. In 50% of cases, pregnancy was terminated due to fetal death following fetal intervention [51].

At present, there are no clear parameters for predicting future renal function. Fetal surgery may be offered in individual cases as an alternative treatment option after detailed consultation with parents [24].

Postnatal treatment. The early stage of surgical treatment for posterior urethral valves involved extensive, traumatic open procedures on the urethra. Along with the valve, the hypertrophied bladder neck was sometimes removed, leading to total urinary incontinence [42]. Kholzov's perineal urethroplasty was performed until the 1990s [2].

The modern era of surgical PUV treatment began with video-endoscopic technologies in pediatric urology. Today, newborns with suspected PUV are monitored in specialized multidisciplinary centers during the prenatal period. In a smaller percentage of cases, PUV is diagnosed at a later age due to the presence of heterogeneous urinary symptoms, such as urinary tract infections, urinary incontinence, a weak urine stream,

and enuresis. It is believed that these patients may have a better renal outcome [13]. However, researchers have not found significant differences in long-term outcomes between patients with early and late diagnosis of PUV. The only real difference between the two groups concerned urinary tract infections, which were more common in the group with postnatal diagnosis [50]. In contrast, data have been published indicating that patients with late diagnosis of PUV have a worse prognosis due to prolonged renal exposure to higher blood pressure [46].

A newborn with suspected PUV requires bladder drainage via transurethral catheterization as the primary intervention at birth. Subsequently, voiding cystourethrography should be performed to confirm the diagnosis, provided that patient's condition permits this examination. Once the patient's condition has stabilized (electrolyte, respiratory, and renal disorders) video-cystoscopy can confirm the results of voiding cystography and transition from a diagnostic procedure to a therapeutic one. Endoscopic ablation or resection of the valve should be performed [21]. Valve ablation in the first few months of life yields better long-term outcomes in terms of urodynamics, vesicoureteral reflux, and improvement or elimination of ureterohydronephrosis [21, 34, 53]. Early valve ablation is not feasible in some newborns due to small urethral caliber. In such cases, gradual urethral dilation should be performed by sequentially replacing urethral catheters with larger ones [53]. Methods for PUV destroying include electrocoagulation, a "cold" knife, or laser incision/fulguration. After valve ablation, a urethral catheter of appropriate diameter is placed in the bladder, and drug therapy with M-cholinoblockers (oxybutynin) is initiated at a dose of 0.2 mg per kilogram three times daily [4, 7].

Urinary diversion. In some cases, primary valve ablation is not possible. Under such circumstances, urinary diversion must be performed using a urethral catheter, suprapubic cystostomy, or temporary vesicostomy. The choice of urinary diversion method remains a matter of debate [34, 45]. Recent studies suggest that vesicostomy does not improve the prognosis or reduce the incidence of renal failure in patients with severe upper urinary tract dysfunction, high-grade vesicoureteral reflux, or recurrent urinary tract infections [45].

Intermittent catheterization. In cases of persistent voiding dysfunction, chronic urinary retention, recurrent urinary tract infections, or persistent bladder-dependent neurogenic bladder dysfunction, patients are recommended to undergo clean intermittent catheterization of the bladder. Studies show that clean intermittent catheterization reduces the frequency of complications associated with neurogenic dysfunction of the valve bladder and stabilizes renal function or delays the need for renal replacement therapy [38].

Augmentation cystoplasty. Regardless of the treatment administered, approximately one-third of patients with a posterior urethral valve develop chronic renal failure [18]. The problem is exacerbated by polyuria and the development of a high-pressure, low-capacity valve bladder [36]. Augmentation cystoplasty allows to create a low-pressure reservoir with sufficient capacity, thereby relieving patients of urinary incontinence and stabilizing or improving renal function, which, in turn, allows to delay or prevent the need for kidney transplantation in these children [10].

Treatment of VUR. Despite the significant prevalence of VUR in PUVs (48–66% [24]), spontaneous resolution of reflux occurs in 27–79% of cases, ranging from 2 weeks to more than one year after valve ablation [26, 43]. The EAU–ESPU guidelines recommend preventive use of antibiotics in boys with severe VUR and PUV [23]. Circumcision may have a beneficial effect on reducing the number of febrile urinary tract infections (UTIs) [25]. When patients have persistent VUR after PUV destruction and experience recurrent episodes of febrile UTIs or progressive renal failure, surgical treatment is indicated (endoscopic correction or ureteral reimplantation) [6, 33]. Early creation of a continent appendicovesicostomy using the Mitrofanov technique may yield good results in patients with a congenital ureteral malformation who develop a manifest urinary tract infection [44].

OUTCOMES

Valve bladder syndrome. The concept of the valve bladder was formulated in the 1980s. It was described as a thick-walled, poorly distensible bladder with high resting pressure, leading to ureterohydronephrosis and renal failure [44]. A series of urodynamic studies in these patients identified three main urodynamic patterns, which represent the progression of the same neurogenic bladder dysfunction, changing with the patients' age [20, 29]. In infants, there is a reduction in functional bladder capacity and detrusor overactivity. Over the next 1–3 years, bladder capacity increases while detrusor hyperactivity persists, and residual urine volume rises. By ages 4–12, bladder capacity also increases, detrusor hyperactivity resolves, detrusor contractility decreases, and residual urine volume increases [47].

Renal failure. In children with VUR, there are two main factors that trigger the development of chronic kidney disease (CKD): impaired nephrogenesis and neurogenic bladder dysfunction, which may persist even after transurethral valve resection [1, 44]. Various studies report that chronic kidney disease develops in approximately 30–50% of patients with PUV. Recent reports from multicenter cohort studies in the United States, involving 274 [38] and 685 [28] patients, have

provided new data on chronic kidney disease (CKD) and end-stage renal disease in children with PUV. By ages 1, 5, and 15 years, 7%, 12%, and 20% of children, respectively, required renal replacement therapy. In another study involving 35 infants, by age 10 years, 50% of children had developed stage II–IV CKD, and 15% required renal replacement therapy [18]. Another study covering the period from 2002 to 2011 found that 11% of children on renal replacement therapy in North America were diagnosed with PUV, highlighting the high social and economic burden of this disease [52]. Although figures vary across different reports, the proportion of patients with CKD (up to 50%) and end-stage renal disease (up to 20%) is sufficiently high to warrant ongoing monitoring by a pediatric nephrologist, including urodynamic studies for all children with PUV. Adverse prognostic factors for the development of CKD include: early onset of PUV, serum creatinine levels exceeding 1 mg/dL, grade III or higher VUR, recurrent febrile urinary tract infections, renal dysplasia, and neurogenic bladder dysfunction [18].

CONCLUSION

Thus, posterior urethral valve is a serious congenital anomaly that can lead to progressive damage involving the kidneys and bladder. Current treatment strategies are based on early diagnosis using prenatal ultrasound and minimally invasive endoscopic ablation of the valve during the first months of life. Despite improved methods for this procedure, a sig-

nificant proportion of patients remain at risk of developing chronic kidney disease and bladder dysfunction, which requires long-term multidisciplinary follow-up. Further research is needed to standardize treatment approaches and improve long-term outcomes in children.

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Hepatobiliary and pancreatic ascariasis. A clinical case of recurrent pancreatitis of parasitic origin in a child

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ABSTRACT

Hepatobiliary and pancreatic ascariasis (HPA) is a rare complication of *Ascaris lumbricoides* infection, one of the most common helminths worldwide. In the Russian Federation, ascariasis is the second most prevalent parasitic disease, and children are the primary risk group. However, HPA as a cause of chronic pancreatitis in pediatrics is extremely rare, with the overall incidence of chronic pancreatitis among children being only about 0.5–1 case per 100,000. This rarity creates significant diagnostic challenges and leads to prolonged unsuccessful treatment. The article describes a clinical case of recurrent chronic pancreatitis in a 6-year-old girl. Over several years, the patient was repeatedly hospitalized with acute biliary pancreatitis. The examination ruled out cholelithiasis, ductal anomalies, and autoimmune or hereditary pancreatitis. During the diagnostic workup, an endoscopic ultrasound-guided fine-needle aspiration biopsy of the pancreas was performed; cytological examination of the aspirate revealed findings consistent with possible parasitic infestation. Despite negative serological tests for ascariasis, key findings included eosinophilia and an endosonographic image of a cluster of cylindrical calcifications in the terminal part of the Wirsung's duct, interpreted as a result of calcification of a dead helminth. This case underscores that in children with idiopathic recurrent pancreatitis, the possibility of a past parasitic infection must be considered. A comprehensive diagnostic approach should include not only serology but also morphological examination and high-resolution imaging of the ductal system.

Keywords: ascariasis, hepatobiliary and pancreatic ascariasis, recurrent pancreatitis

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Гепатобилиарный и панкреатический аскаридоз. Клинический случай рецидивирующего панкреатита паразитарного происхождения у ребенка

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РЕЗЮМЕ

Гепатобилиарный и панкреатический аскаридоз (ГПА) — редкое осложнение инвазии *Ascaris lumbricoides*, одного из самых распространенных гельминтов в мире. В Российской Федерации аскаридоз является вторым по распространенности паразитарным заболеванием, а в группе риска — дети. Однако ГПА как причина хронического панкреатита в педиатрии встречается крайне редко, а общая заболеваемость хроническим панкреатитом среди детей составляет всего около 0,5–1 случая на 100 тысяч, что создает значительные диагностические трудности и приводит к длительному безуспешному лечению. В статье описан клинический случай рецидивирующего хронического панкреатита у девочки 6 лет. На протяжении нескольких лет пациентка неоднократно госпитализировалась с картиной острого билиарнозависимого панкреатита. При обследовании были исключены желчнокаменная болезнь, аномалии развития протоков, аутоиммунный и наследственный панкреатит. В ходе диагностики была выполнена тонкоигольная биопсия поджелудочной железы под эндосонографическим контролем. Цитологическое исследование пунктата выявило картину, не исключавшую паразитарное поражение. Несмотря на отрицательные серологические тесты на аскаридоз, ключевыми находками стали эозинофилия и эндосонографическая картина скопления цилиндрических кальцинатов в терминальном отделе вирсунгова протока, интерпретированная как результат кальцификации погибшего гельминта. Данное наблюдение подчеркивает, что при идиопатическом рецидивирующем панкреатите у детей необходимо учитывать вероятность перенесенной паразитарной инвазии. Комплексный поиск должен включать не только серологическое, но и морфологическое исследование, а также высокоразрешающие методы визуализации протоковой системы.

Ключевые слова: аскаридоз, гепатобилиарный и панкреатический аскаридоз, рецидивирующий панкреатит

Как цитировать

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INTRODUCTION

According to the World Health Organization, more than 1.4 billion people worldwide are infected with ascariasis. Preschool and school-age children make up the majority of these cases. Each year, up to 20,000 people die from ascariasis and its complications. In Russia, ascariasis is the second most common helminthiasis after enterobiasis. In the United States, approximately 4 million people are infected, with the majority of those infected being immigrants from developing countries. Ascariasis is widespread throughout the Indian subcontinent, China, the African continent, and Latin America [3, 6]. The highest prevalence of ascariasis is recorded in developing countries with poor sanitary and epidemiological conditions. The list of diseases that can be caused by ascariasis is quite extensive. These include protein-calorie malnutrition, total vitamin deficiency, pneumonia, Leffler's syndrome, toxic-allergic reactions, sinusitis, frontal sinusitis, intussusception, appendicitis, intestinal obstruction, meningism, and hepatobiliary and pancreatic ascariasis (HPA) [4, 5]. Kashmir, India, and Colombia, Saudi Arabia, Syria, the Philippines, and South Africa are endemic for ascariasis, and in particular for HPA. Sporadic cases of HPA have been reported in Italy, Spain, Switzerland, and Lithuania [6, 10, 11, 14]. HPA is caused by the nematode *Ascaris lumbricoide*, that is one of the most common intestinal parasites in the world. Its clinical manifestations include biliary colic, cholangitis, cholecystitis, acute pancreatitis, and, rarely, liver abscess. Biliary peritonitis has also been reported [6]. HPA is more common in adult patients and pregnant women; it is significantly less common in children, due to the smaller size of the ducts and the duodenal papilla [6].

Ascariasis has been reported among residents of America, Asia, and Europe as a result of infection with another species of nematode from the genus *Ascaris* — *A. suum*. Since it is virtually impossible to distinguish the eggs of these two species under a microscope, and the adult worms are similar, the prevalence of *A. suum* infection remains unknown. In the case of *A. suum*, human infection can occur from pigs when pig manure is used as fertilizer [11].

The sole host of *Ascaris lumbricoides* is the human. Immature eggs are excreted into the environment with the feces of an infected person, and under favorable conditions, larvae mature. Egg maturation occurs at temperatures of at least 12 °C, soil moisture of at least 8%, and free access to oxygen. The mechanism of human infection involves eggs entering the mouth along with soil particles. Transmission factors: contaminated water, dirty hands and food (unwashed berries, leafy vegetables, and root vegetables). This explains the highest prevalence of ascariasis among preschool-aged children, individuals living in poor sanitary and epidemiological conditions,

and rural residents. A case of transplacental migration of larvae from mother to fetus has been described [11]. Helminth eggs can survive in soil for up to 10 years and in freshwater reservoirs for up to one year. In temperate climates, ascarid eggs can withstand temperatures as low as –25 °C, and the peak incidence period lasts from April to October. In warm and humid climates, prevalence remains high year-round. Swallowed ascaris eggs enter the human small intestine, where larvae hatch and burrow into the intestinal wall, penetrate the blood vessels, and migrate through the liver into the inferior vena cava. Via the right side of the heart, the larvae are carried by the bloodstream into the pulmonary vessels and enter the lung parenchyma. Eosinophilic infiltrates develop in the lung tissue. Here they grow, molt, and after 14 days travel along the epithelium of the alveoli and bronchioles, as well as the small and large bronchi, up to the oropharynx, where they are swallowed with saliva. Once back in the small intestine, they grow for 70–75 days and develop into males and females [2, 4, 14].

There are several key aspects to the pathogenesis of ascariasis: mechanical damage to tissues and blood vessels caused by larvae, activation of local inflammation, sensitization to parasite's metabolic byproducts, depletion of host's nutrients, and the development of hypovitaminosis, impaired digestion due to a reduced surface area for food digestion, disrupted passage of the bolus, molting, and the decomposition of dead worms. In the vast majority of cases, the immunity that develops is short-lived, unstable, and does not prevent reinfection [2, 6].

Sexual dimorphism is characteristic for ascaris. Males reach 15 cm in length and 4 mm in diameter; the posterior end of their body is curved. Live worms are pink; they turn milky-white when they die. Female roundworms can reach 30 cm in length and 6 mm in width. The lifespan of an adult roundworm is approximately one year. A mature female lays up to 200–245 thousand eggs per day [2, 3, 6].

HPA develops when an ascarid crawls through the orifice of the major duodenal papilla into the common bile duct, creating a mechanical obstruction for the outflow of bile and pancreatic juice. Patients with HPA often undergo a long journey from the onset of acute pancreatitis to confirming the infection and eliminating the cause of recurrent pancreatitis. Diagnosis is difficult because the worm can migrate from the ductal system back into the intestine and remain undetected by imaging for a long time. An adult worm is capable of obstructing both the common bile duct and the pancreatic duct. Additionally, the worm's movements cause severe spasm of the sphincter of Oddi and impaired motility. When they enter the bile duct and move upward, *Ascaris* worms cause obstructive cholecystitis, cholangitis, and obstructive jaundice. The worm can migrate into hepatic ducts, more

often into the left ones. Cases of suppurative cholangitis and liver abscess have been reported in such patients. Roundworms penetrate pancreatic ducts significantly less frequently. Researchers believe that the worm can remain alive in the biliary tract for about 10 days. After this period, the parasite should be considered dead. Dead roundworms also pose a danger since they serve as a substrate for stone formation. The development of local inflammation and formation of stones are also facilitated by intestinal microorganisms, which enter the bile ducts along with the ascaris [6, 8].

Clinical forms of HPA include biliary colic, acute cholangitis, non-calculous cholecystitis, liver abscess, acute pancreatitis, and recurrent suppurative cholangitis [6, 7, 10]. Patients may complain of nausea and vomiting, pain in the right upper quadrant, and chills. Fever, jaundice, hepatomegaly, hyperenzymemia (elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase), leukocytosis, and hyperbilirubinemia may occur. When acute pancreatitis develops, girdle-like pain radiating to the back and elevated levels of amylase and lipase in the blood appear. Fatal cases of necrotizing and hemorrhagic pancreatitis resulting from *Ascaris* infestation have been reported. Most patients with parasitic infestation exhibit eosinophilia. When taking a medical history, attention should be paid to patients' visits to endemic regions, consumption of unwashed berries or vegetables, and the appearance of nonspecific symptoms such as weight loss, weakness, rapid fatigue, and bowel disturbances. In patients with concomitant allergic conditions, parasitic infestation may trigger an exacerbation of the underlying disease [3, 6, 10, 14].

Endoscopic ultrasound (EUS) is currently considered the most informative method for diagnosing HPA [6]. However, this method also yields up to 30% false-negative results. The ultrasonographic picture consists of single or multiple linear hyperechoic structures without an acoustic shadow in the pancreatic duct or common bile duct, with a central hypoechoic tube representing the worm's digestive tract. Worm movements within the duct, the so-called "four-line phenomenon", may also be observed. An important aspect is that endoscopic ultrasonography allows for immediate therapeutic measures to remove the worms. According to a number of researchers, endoscopic retrograde cholangiopancreatography (ERCP) lags behind EUS in terms of diagnostic accuracy when it comes to invasion of the common bile duct, gallbladder, and hepatic bile ducts. However, the opposite is true when it comes to infestations of the pancreatic ducts. In such cases, ERCP has a clear advantage, as the worm is visualized as a smooth, long filling defect. Magnetic resonance cholangiopancreatography (MRCP) is also considered a highly accurate method, but it does not al-

low for immediate therapeutic intervention upon detection of the parasite. For dynamic monitoring of patients and assessment of treatment efficacy, ultrasound methods are preferred [6, 12].

Treatment for HPA includes antiparasitic drugs, antispasmodics, analgesics, and broad-spectrum antibiotics. Albendazole is considered the drug of choice among antiparasitic agents, and its efficacy is enhanced when taken with fatty foods. Mebendazole and pyrantel are also used. Mebendazole is metabolized in the liver to an inactive metabolite and is insufficiently effective against helminths in the gallbladder and ducts [3, 4, 8]. It remains controversial whether anthelmintic therapy can be administered while the worm are the ducts. Attempts have been described to manage patients conservatively without antiparasitic therapy to prevent worms from dying in the ductal system [13]. The use of anthelmintic drugs is ineffective against larvae as well. Even mild cases of *Ascaris* infection should be treated to prevent complications caused by parasite migration; however, during active migration through the lungs, drug therapy is not indicated due to the increased risk of pneumonitis. Antiparasitic solutions should not be instilled into the biliary tract to avoid worm disintegration and progression of inflammation [9]. There is no single standard of care for patients with biliary ascariasis. Some authors believe that endoscopic therapy for biliary ascariasis is indicated if patients continue to experience symptoms despite drug therapy or when worms do not exit the duct lumen within three weeks or die within the ducts [6, 14]. Other authors believe that endoscopic therapy should be performed immediately upon detection of helminths in the gallbladder or ducts [8]. A number of authors suggest a wait-and-see approach for 72 hours from the start of conservative treatment. If clinical manifestations and the ultrasonographic picture of HPA remain, ERCP should be performed for therapeutic purposes. Sphincterotomy may contribute to repeated migration of worms into the biliary tract. For this reason, balloon dilation of the sphincter of Oddi is preferred. The worms should be removed completely, as residual fragments may lead to stone formation. Removal of the worms is usually associated with rapid relief of clinical symptoms [9]. If the endoscopic method is ineffective, surgical treatment is indicated.

CLINICAL CASE

A 6-year-old girl with food allergies was admitted to the hospital. She complained of severe abdominal pain, nausea, and repeated vomiting. Laboratory tests revealed elevated ALT levels (up to 658 U/L), AST levels (up to 760 U/L), total bilirubin (up to 33 $\mu\text{mol/L}$), and serum amylase (up to 1566 U/L). A multi-slice computed tomography (MSCT) scan of the abdominal organs revealed: dilatation of the intrahepatic ducts and common bile duct

up to 9 mm, a calculus up to 8 mm at the junction of the common bile duct and the pancreatic duct, dilatation of the gallbladder and its walls, and enlargement of the pancreas due to the head up to 35 mm. Magnetic resonance cholangiopancreatography (MRCP) was performed. It revealed signs of narrowing at the opening and dilation of the common bile duct throughout its length. Diagnosis: Acute biliary pancreatocholangitis, gallstone disease. Treatment was conducted in a hospital setting and included antibiotics, antispasmodics, and H₂-histamine blockers; infusion therapy was also administered. During the outpatient phase of treatment, the patient received enzyme preparations and ursodeoxycholic acid courses. Elevated amylase levels persisted for a long time, reaching 2–3 times normal levels.

A year later, a relapse occurred; the girl was admitted with paroxysmal abdominal pain and repeated vomiting, elevated serum amylase levels up to 5,000 U/L, and ALT and AST levels up to 250 U/L. Bilirubin levels fluctuated up to 180 μ mol/L. The results of a MSCT scan of abdomen showed: enlargement of the pancreatic head, dilation of the main pancreatic duct to 11 mm, dilation of the lobular ducts to 7 mm, and cystic transformation of the gallbladder. After treatment, no relapses were observed for 2 years, and the patient remained under follow-up. Laboratory tests showed periodic elevations in serum amylase up to twice the normal level. The patient followed a strict low-fat diet and received pancreatic enzymes and ursodeoxycholic acid.

The third episode of pancreatitis occurred at age 9. The girl was admitted with acute abdominal pain and elevated amylase levels of 1186 U/L. MSCT revealed enlargement and diffuse changes in the pancreatic head. Cholesterol stones in the gallbladder (Fig. 1). It was decided to perform surgical treatment. A common bile duct cyst was removed, and a Roux-en-Y choledochojejunostomy was performed.

In the postoperative period, signs of pancreatitis were noted; otherwise, the course was uneventful. During a follow-up examination in the late postoperative period, dilation of the intrahepatic ducts was detected, although it was less pronounced than before. Dilation of the Wirsung and Santorini ducts was confirmed by MRCP.

One and a half years after the surgical procedure, the patient was readmitted with an exacerbation of pancreatitis. Elevated blood pancreatic amylase levels reaching 2000 U/L were detected. Due to severe condition, the patient was admitted to the intensive care unit and received infusion therapy, octreotide, amikacin, metronidazole, antispasmodics, and analgesics, following which amylase levels decreased. An increase

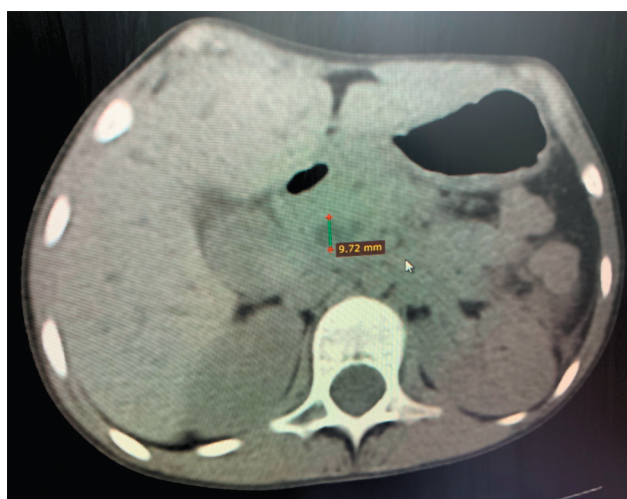


Fig. 1. Abdominal CT scan. Enlargement and diffuse changes of the pancreatic head. Gallbladder cholesterosis, cystic transformation of the common bile duct

Рис. 1. Мультиспиральная компьютерная томография органов брюшной полости. Увеличение и диффузные изменения головки поджелудочной железы. Холестероз желчного пузыря, кистозная трансформация холедоха

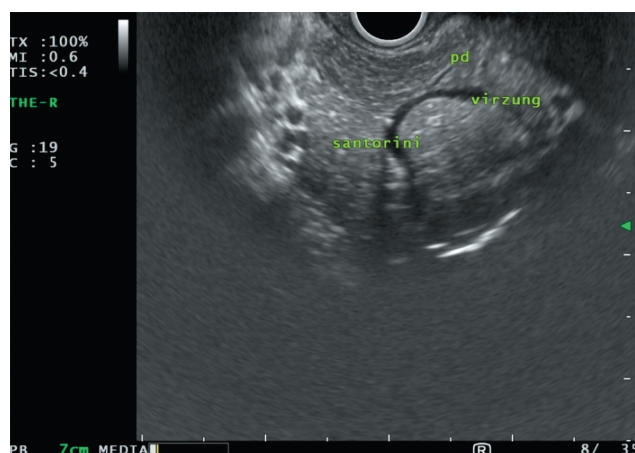


Fig. 2. Endosonographic signs of calculi in the terminal part of the Wirsung's duct (hyperechoic inclusions measuring 5–7 mm extending for approximately 1.5 cm, with a distinct acoustic shadow) and pancreatic hypertension

Рис. 2. Эндосонографические признаки конкрементов терминального отдела вирсунгова протока (гиперэхогенные включения до 5–7 мм на протяжении около 1,5 см, с четкой акустической тенью), панкреатической гипертензии

in serum lipase to 886 U/L was also observed. Eosinophilia was noted. A CT scan of the abdominal organs revealed enlargement and calcification of the pancreatic head, dilation of the bile ducts and pancreatic ducts, and fluid accumulation in the abdominal cavity between the loops of the small intestine. Endoscopic retrograde cholangiopancreatography (ERCP) revealed dilation of the Wirsung and Santorini ducts, as well as irregularity in the diameter of the intrahepatic ducts. Endosonography revealed calculi in the terminal portion of the Wirsung duct and pancreatic hypertension (Fig. 2). During endoscopic ultrasonography, a fine-needle biopsy of the pancreas was performed.

Cytohistological examination of the pancreatic tissue aspirate showed that the material consisted primarily of a dense proteinaceous substance, microcalcifications, blood cells, and a small number of epithelial cells with proliferation but no mitotic activity. No evidence of neoplastic lesions was found in the examined material. This pattern did not rule out a parasitic infection. Enzyme-linked immunosorbent assay (ELISA) of blood for antibodies to *Ascaris*, *Giardia*, *Anisakis*, and *Toxocara* was negative. An elevated level of IgG4 in the blood was noted, which required additional testing for differential diagnosis between obstructive and autoimmune pancreatitis.

Subsequent routine follow-up examinations were performed. Endosonography revealed a cluster of cylindrical calcifications with a distinct acoustic shadow in the terminal portion of the Wirsung duct, obstructing the duct (Fig. 3). An aspiration biopsy of the pancreatic head tissue was performed, followed by immunohistochemical examination of the specimen. No evidence of atypia or active inflammation was found. No immunohistochemical signs of autoimmune pancreatitis were

detected. Since obstruction and chronic pancreatitis (gallstone disease, autoimmune pancreatitis, tumor) were excluded, it was suggested, that the patient had HPA complicated by the death of the helminth in the duct and subsequent calcification, based on the clinical and anamnestic data and the course of the disease involving cylindrical calcifications in the Wirsung duct.

During subsequent follow-up over a three-year period, no exacerbations of pancreatitis were observed. The patient is continuously receiving pancreatic enzyme therapy at a dose of 500 IU of lipase per kilogram per day. According to the results of the most recent hospitalization in September 2024, fecal elastase was 284.39 µg/g, urine alpha-amylase was 253 U/L (normal range up to 321 U/L), and serum alpha-amylase was 30.1 U/L (normal range up to 80 U/L). According to abdominal CT scan data, changes in the pancreas persist, including enlargement, structural heterogeneity due to areas of calcification in the head region, dilation of the Wirsung duct to 3 mm, and thickening of the peripancreatic tissue. Over time, a slight decrease in the size of the pancreas is noted. Further observation, laboratory testing, and imaging studies are required to monitor the patient's condition.

CONCLUSION

This clinical case report presents a complex and atypical case of chronic recurrent pancreatitis in a child, which probably had parasitic origins. Its diagnostic feature combines indirect signs of infestation with direct morphological confirmation: against the background of negative serological tests and the absence of live parasite visualization, the cytological examination of the pancreatic puncture, which revealed signs of parasitic involvement, was of key importance. This finding, along with eosinophilia and a unique endosonographic pattern of cylindrical calcifications clustered in the Wirsung duct, allows us to conclude that the process was caused by the death and further calcification of an *Ascaris* worm. Subsequently, it formed an obstructing calculus. This case clearly illustrates that HPA can present as idiopathic pancreatitis with a long-term, indolent course and recurrences even after surgical correction of secondary complications. This observation underscores the need for active investigation of parasitic causes in children with recurrent pancreatitis of unknown etiology. It also demonstrates the high diagnostic value of combining endosonography with targeted morphological verification to identify both direct and indirect consequences of invasion.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, draf-

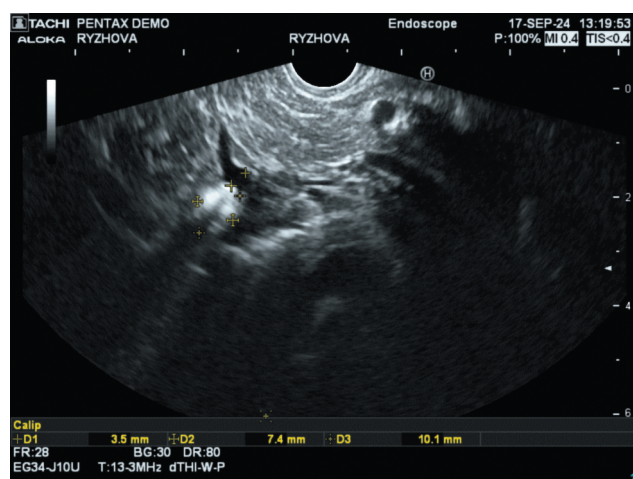


Fig. 3. Endosonographic signs of hyperechoic calculi with a distinct acoustic shadow in the terminal part of the Wirsung's duct, indicating pancreatic hypertension

Рис. 3. Эндосонографические признаки скопления гиперэхогенных конкрементов с четкой акустической тенью в терминальном отделе вирсунгова протока, панкреатической гипертензии

ting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The author declares that he has no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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Вклад авторов. Все авторы внесли существенный вклад в концепцию исследования, сбор, анализ,

интерпретацию данных для работы, составление и пересмотр статьи, окончательное утверждение версии для публикации и соглашаются нести ответственность за все аспекты исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Wilhelm Conrad Röntgen: the man who saw the invisible. On the 180th anniversary of his birth and the 130th anniversary of the discovery of X-rays

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ABSTRACT

The article explores the life and scientific achievement of Wilhelm Conrad Röntgen (1845–1923), the outstanding experimental physicist who discovered X-rays and transformed the course of modern science and medicine. It traces Röntgen's path from his unjust expulsion from school and the difficulties of his early education to his later leadership of major physics institutions in Germany, where he developed into a scientist whose work shaped experimental physics for decades to come.

Particular attention is devoted to the circumstances of his November 1895 discovery of a new type of radiation capable of penetrating opaque materials and revealing the internal structure of the human body without surgical intervention. The article highlights Röntgen's meticulous experimental approach, his long days and nights of isolated work, and his determination to investigate every hypothesis in order to understand the nature of the mysterious rays that had no precedent in science.

A central theme is Röntgen's principled decision to refuse a patent for his discovery. Believing that such knowledge must serve humanity, he deliberately made the new radiation freely available, enabling its rapid adoption in medical diagnostics and ultimately saving millions of lives.

The material presents Röntgen not only as a brilliant experimenter but also as a man of exceptional moral integrity, for whom scientific truth and public good outweighed personal benefit. His legacy — an embodiment of talent, perseverance, and ethical conviction — continues to define the development of physics and medicine to this day.

Keywords: Wilhelm Röntgen, discovery of X-rays, history of science, Nobel Prize in Physics, cathode rays, X-ray image, scientific ethics, biography of a scientist

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Вильгельм Конрад Рентген: человек, который увидел невидимое. К 180-летию со дня рождения и 130-летию открытия рентгеновских лучей

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РЕЗЮМЕ

Статья посвящена жизни и научному подвигу Вильгельма Конрада Рентгена (1845–1923), выдающегося физика-экспериментатора и первооткрывателя X-лучей, которые стали одним из величайших достижений мировой науки. В работе прослеживается путь Рентгена — от несправедливого изгнания из школы и трудностей раннего образования до руководства крупнейшими физическими институтами Германии, где он сформировался как ученый, определивший направление развития экспериментальной физики на десятилетия вперед.

Особое внимание уделено обстоятельствам открытия в ноябре 1895 года нового типа излучения, способного проникать сквозь непрозрачные материалы и впервые в истории позволившего увидеть внутреннее строение человеческого организма без операции. Подробно рассматриваются экспериментальные поиски Рентгена, его многодневная работа в изоляции, стремление проверить каждую гипотезу и установить природу лучей, которые на тот момент не имели аналогов в науке.

Отмечается принципиальная позиция ученого, категорически отказавшегося патентовать свое открытие, поскольку он считал, что подобное излучение должно служить всему человечеству. Его решение открыло путь к стремительному развитию медицинской диагностики и спасло миллионы жизней по всему миру.

Материал позволяет увидеть в Рентгене не только гениального экспериментатора, но и человека высочайших моральных принципов, для которого научная истина и общественное благо стояли выше личной выгоды. Его наследие, олицетворяющее соединение таланта, упорства и этики, продолжает определять развитие медицины и физики и сегодня.

Ключевые слова: Вильгельм Рентген, открытие рентгеновских лучей, история науки, Нобелевская премия по физике, рентгеновский снимок, научная этика, биография ученого

Как цитировать

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Genius may be nothing more than a fleeting opportunity.

Only hard work and determination can bring it to life and turn it into glory.

Albert Camus

Throughout history, some people have been born with the ability to perceive the world differently. They see it from a unique perspective, discern what remains hidden from others, and shed light on what still lies in darkness. These individuals are key contributors to progress; thanks to them, humanity has evolved into a civilization, and science continues to make new strides every year. It seems that fate itself guides such people: every encounter, every event comes together to form a path leading to a great discovery (Fig. 1).

It was precisely such a person who was born on March 27, 1845, in the small town of Lennep to Friedrich Conrad Röntgen and Charlotte Constance. The boy was named Wilhelm Conrad. His mother came from the ancient Frowein family, which lived in Holland, and his father belonged to a respected merchant dynasty whose roots stretched far back into the lands along the Rhine.

In 1848, the French Revolution erupted, its echoes reaching as far as Prussia. Röntgen's father sold the family home and moved with his family to the Netherlands. Thus, three-year-old Wilhelm unexpectedly became Dutch. Nevertheless, as he began a new life in a foreign land, he forever kept the house in Lennep in his heart: he recalled every corner of it with particular tenderness and sadness, where he had spent the most carefree years of his childhood.

In 1850, the Röntgen family settled in Apeldoorn, in a house that came to symbolize their love and

hopes. They engraved the name of their five-year-old son, Wilhelm, on the south wall. This touching gesture speaks volumes about parents' feelings: they were not simply furnishing a home, but creating a space where their only and dearly beloved son could grow up to be a decent person.

Wilhelm Röntgen spent fourteen years in this house, while attending the school of Martinus Hermanus van Doorn. In 1862, the family moved to Utrecht. At nearly eighteen years old, Wilhelm Conrad moved in with Dr. Hanning, a Utrecht chemist who taught at both the university and the technical school.

The Utrecht Technical School accepted boys aged 14 to 18, training them to become future managers of factories and enterprises. At first, a quite predictable path lay ahead for Röntgen as well. He would continue the family business and get involved in textile manufacturing. But fate had other plans. In early 1865, his mentor, Dr. Jan Hanning, was appointed professor of chemistry in Amsterdam. This was a turning point for the young Wilhelm: he increasingly realized that he was drawn to natural sciences.

Röntgen was a gifted student and easily mastered most subjects, except for physics. It was taught by Ger Patterson, a man who disliked Wilhelm from the very beginning, and the feeling was mutual. The story ended in a sad misunderstanding: one of his classmates drew a caricature of the teacher on a piece of paper, but the blame fell on Röntgen. He did not reveal the real culprit and paid a high price for his silence — at the age of seventeen, he was expelled from school [1].

Wilhelm Röntgen weathered this stroke of fate with his characteristic nobility and fortitude, even though the lack of a high school diploma hindered his admission to university. His father supported his son: "It's all right; three generations of men in our family have been cloth manufacturers, and you will make an excellent cloth maker".

But Röntgen decided not to give up; his innate tenacity and determination prevailed. He began preparing himself for exams to Utrecht University. However, due to a cruel twist of fate, his math exam was proctored by none other than Ger Patterson, who was filling in for a professor who had unexpectedly fallen ill. And he failed the exam.

It is no surprise that after such trials, Röntgen viewed exams with a touch of irony for the rest of his life. In 1920, he wrote to Mrs. Boveri, the daughter of his friend, the biologist Theodor Boveri, whose ideas anticipated modern mutation theory: "Student exams, as a rule, do not reveal true aptitude for a subject. Unfortunately, they are a necessary evil. The true test of aptitude for a profession comes only in adulthood".

However, Wilhelm Röntgen did not give up this time either. Four days after his failure, he enrolled in the



Fig. 1. Portrait of Wilhelm Conrad Röntgen. 1900 (Photograph. Public domain)

Рис. 1. Портрет Вильгельма Конрада Рентгена. 1900 г. (Фотография. Общественное достояние)

philosophy department, which accepted students without strict high school diploma requirements. However, philosophy alone was not enough. He was too drawn to natural sciences. In 1865, by a stroke of good fortune, the Polytechnic Institute opened in Zurich, where one could enroll without a high school diploma, simply by passing exams in mathematics, Ancient Greek, and Latin. Röntgen was admitted, exempted from the language exams as his exceptional knowledge of mathematics impressed the examiners. Thus, the twenty-year-old young man became a student at the institute that would shape his scientific destiny.

During his student years, Röntgen and his friends would gather in the evenings at the “Green Glass” café. There he met Bertha Ludwig, the daughter of the café’s owner. Seven years later, this meeting culminated in their marriage.

His acquaintance with Professor August Kundt proved no less significant. After hiring Röntgen as his laboratory assistant, Kundt once asked him a question that would prove fateful: “What do you really want to do with your life?” This question compelled Röntgen to finally define his path in science.

Not receiving a precise answer, the professor advised: “Start doing science — it’s never too late”. For Röntgen, Kundt was not merely a mentor, but a true guide into the world of physics. He managed to instill in the young researcher a love for experimentation, patience in his work, and the ability to build instruments on his own. It was alongside Kundt that Röntgen got a taste of genuine scientific inquiry and finally found his calling to become an experimental physicist [2].

In 1870, August Kundt was appointed to the University of Würzburg, and invited his loyal assistant, the young Wilhelm Röntgen, to join him. There, Röntgen began work on his dissertation, but the university dean rejected it for unknown reasons. These difficulties were temporary: soon Kundt was transferred to the Imperial University of Strasbourg, and Röntgen, of course, followed him. There, in 1874, Röntgen was appointed a private lecturer at the Institute of Physics.

The young scientist’s career continued to advance. Thanks to a recommendation from Heinrich Weber, a former professor at the academy, Röntgen was appointed professor of physics and mathematics at the Agricultural Academy in Hohenheim. However, as early as 1876, he returned to Strasbourg to take up a position as a lecturer in physics. Although Röntgen had to teach theoretical physics, it was his years in Strasbourg that revealed his true calling. His research at that time was distinguished by a clear formulation of problems, the elegance of his experimental techniques, and a rare ability to analyze results with clear-headedness and depth.

From that point on, Wilhelm’s circle of acquaintances expanded; he met the biologist Georg Gafki, an outstanding German physician and bacteriologist, a close associate of Robert Koch, and the surgeon Rudolf-Friedrich Krenelin, one of the pioneers of appendectomy in Europe and a surgeon who developed and refined his own technique for gastric resection. Getting to know such outstanding scientists significantly broadened Röntgen’s scientific horizons and had a beneficial influence on his work.

But Röntgen never forgot about his family. Although the couple had no children of their own, they adopted Bertha’s niece, Josephine Ludwig. Wilhelm was a caring husband and became a true father to the girl [3].

While in Giessen, he wrote a number of papers, one of which was titled “On the Electrodynamical Force Caused by the Movement of a Dielectric in a Homogeneous Electric Field”. Röntgen demonstrated that free charges located at the interface of an electrically polarized dielectric, namely on the surface of the insulator within a capacitor, also generate an electric current during mechanical motion and are surrounded by a magnetic field. For this purpose, he caused the dielectric to rotate between the plates of a charged capacitor and was thus able to experimentally prove the validity of Maxwell’s first equation.

This work aroused particular interest among scientists of the time. Ludwig Zender, a research associate at the Massachusetts Institute of Technology, wrote: “This discovery by Röntgen was valued by theoretical scientists such as Lorentz, Sommerfeld, and others almost as highly as his discovery of X-rays” [4].

On October 1, 1888, Röntgen received an offer to take up a professorship in Würzburg, succeeding the renowned physicist Friedrich Kohlrausch (1840–1910). Thus, he returned to where his journey had once begun. But now Röntgen was returning not as a student, but as a recognized scientist and an outstanding experimenter. He had reached this pinnacle through his own hard work and talent. During this period, he began studying the effect of pressure on various properties of liquids. Based on the anomaly of water (the presence of maximum density at 4 °C), he concluded that water consists of two different molecular structures: a more voluminous ice structure and structures of smaller volume that are formed only at higher temperatures.

Wilhelm Röntgen was a strict and demanding mentor, both to himself and to his students. He disliked formal exams and preferred to assess his students’ genuine depth of understanding. This approach often put those who were accustomed to rote memorization, rather than a true grasp of science, in a difficult position.

Despite his numerous responsibilities, Röntgen actively pursued scientific research. From 1888 to 1894, he published 50 papers on how pressure affects the properties

of liquids. At the same time, his attention was drawn to cathode rays in gas discharge tubes. The scientist believed that this phenomenon had not been sufficiently studied and devoted a great deal of time to its investigation. By the end of 1895, he was conducting experiments with a modified gas-discharge tube located directly beneath his apartment as he did not like to waste time. At that time, he did not yet know that he was on the verge of his greatest discovery [5].

The history of science is full of examples where the greatest discoveries arose from chance. Such was the case with Wilhelm Röntgen. On the evening of November 8, 1895, he was about to have dinner with his family when, after closing the curtains and covering the cathode tube with cardboard, he absentmindedly failed to turn it off. Turning around at the doorway, he noticed a strange glow: a sheet of paper with barium salt was glowing green, even though there was no light source nearby. The scientist instantly realized — he was facing a phenomenon of unknown nature. Röntgen returned to the laboratory and no longer allowed anyone to enter; he instructed his wife to bring food only and leave it outside the door. He decided to dig up the truth, working day and night, resting only a couple of hours a day. For 50 days, no one saw the scientist, and he experimented with the rays, passing them through all the objects in the laboratory (Fig. 2). “Having learned of an entirely new type of rays, I naturally began to investigate what they would do... Soon, the tests revealed that the rays possessed a penetrating power of a previously unknown degree”, wrote Wilhelm Röntgen [6].

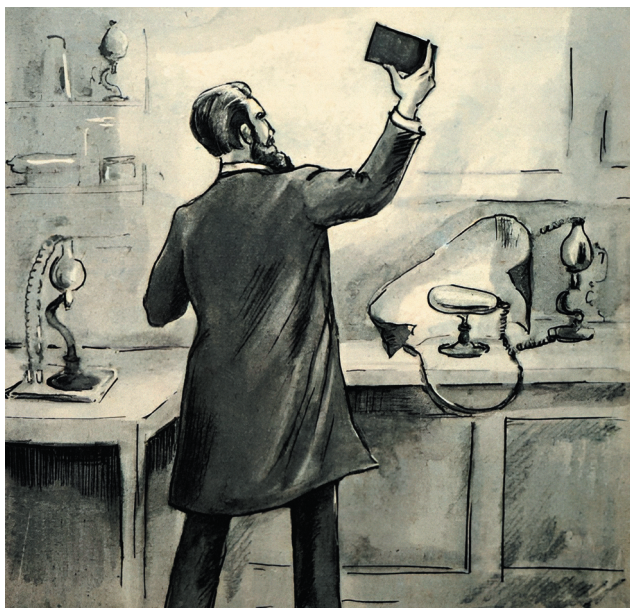


Fig. 2. Artistic illustration: Wilhelm Conrad Röntgen in his laboratory at the moment of discovering X-rays. Late XIX – early XX century (public domain)

Рис. 2. Художественная иллюстрация: Вильгельм Конрад Рентген в лаборатории во время открытия X-лучей. Конец XIX — начало XX века (общественное достояние)



Fig. 3. The first X-ray image — the hand of Anna Bertha Ludwig with a ring on her ring finger. W.C. Röntgen, 8 November 1895. Physical Institute of the University of Würzburg (public domain)

Рис. 3. Первая рентгенограмма — кисть Анны Берты Людвиг с кольцом на безымянном пальце. В.К. Рентген, 8 ноября 1895 года. Физический институт Вюрцбургского университета (общественное достояние)

The great immunologist Louis Pasteur said: to restrain oneself and not announce a discovery until all hypotheses have been tested is a difficult task. These words describe Wilhelm Röntgen very accurately. Immersed in the study of the mysterious rays, he worked late into the night, sacrificing sleep and his health.

His wife was worried about her husband's health, as he hadn't seen daylight for many days. “How long will this go on?” she asked him. “As long as it takes”, Röntgen replied. After seven weeks of experiments, he called his wife into the laboratory and took an X-ray of her hand. Seeing the image of her own bones on the plate, Bertha cried out in horror: “I have seen my own death”. It was the world's first X-ray [7].

On January 5, 1896, a sensation shook the readers of the Viennese newspaper *Die Presse*. The front page reported that on November 8, 1895, a certain Professor Röntgen had discovered a new type of radiation capable of penetrating opaque materials and even allowing one to see through the human body. But how did the story get into the newspaper? During a discussion evening, Professor Franz Exner (Röntgen's colleague and friend) brought a special edition of Röntgen's work, as well as a photograph of a human hand in which the bones, joints, and even a ring on the ring finger were clearly visible (Fig. 3).

Soon, the whole world heard about Röntgen's great discovery. Everyone was stunned, except the scientist himself, who was convinced that sensationalism was merely a “pastime of vanity”, whereas true science

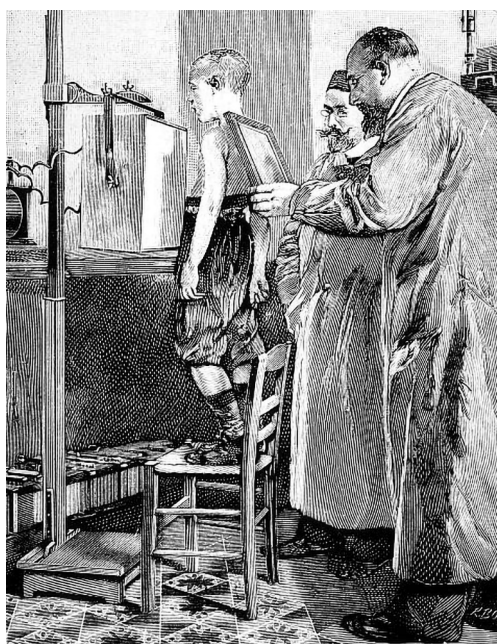


Fig. 4. Artistic engraving: Wilhelm Conrad Röntgen demonstrating the use of X-rays to examine a young boy. Late XIX century (public domain)

Рис. 4. Художественная гравюра: Вильгельм Конрад Рентген демонстрирует применение X-лучей для обследования мальчика. Конец XIX века (общественное достояние)

requires modesty. He refused to patent the discovery, declaring: "My discovery belongs to the people!" The significance of X-rays proved to be enormous: for the first time, medicine gained the ability to look inside the human body without surgical intervention, and soon the first radiology laboratories appeared, including in Russia [8].

Since ordinary people knew absolutely nothing about the nature of the rays, a very funny incident occurred. Once, Wilhelm Röntgen received a letter from a sailor who asked the scientist to send him some X-rays so he could locate a bullet in his chest, to which Röntgen replied: "Unfortunately, sending the rays would be difficult, but there is an easier way: send me your chest, I will find the bullet and send it back to you" [9].

Röntgen categorically refused to allow the military use of his discovery. When asked to use the rays for military purposes, he replied to the Kaiser himself, Wilhelm II: "It is impermissible and inhumane to use for military purposes a means that is needed by sick people". Ironically, the Kaiser fell down the stairs and sprained his leg; for this reason, he had to agree with Röntgen's opinion and use the invention for medical purposes.

Wilhelm Röntgen was a man of rare nobility and humanity: he dedicated all his work to serving science and people, believing that a scientist's mission is "to make the world a better place" (Fig. 4). He shunned fame, disliked interviews, and rarely left his home, as if ashamed of the public attention that had descended upon him following his discovery. In 1900, Röntgen moved to Munich, where he took up a professorship at

the university and headed the Munich Institute of Physics [10].

In 1901, Wilhelm Röntgen became the first recipient of the Nobel Prize in Physics. However, being a modest man, he declined to give a public speech and refused honorary titles, so the prize was sent to him by mail. The Nobel Prize Committee's letter stated: "In recognition of his extraordinarily important contributions to science, manifested in the discovery of the remarkable rays subsequently named in his honor".

He also declined an honorary position at the German Academy of Sciences, and shortly thereafter, the noble title "von". Whenever someone addressed him as Dr. von Röntgen, the scientist would correct them indignantly: "Since I have not yet submitted a special application and do not intend to do so, it is not proper for me to bear the prefix 'von'".

Munich became the final stop in Wilhelm Conrad Röntgen's life. In 1900, he became head of the physics department at Ludwig Maximilian University. In 1903, a young Russian scientist, Abram Ioffe, came to him for an internship; he soon became Röntgen's assistant and one of his few close friends. Their collaboration marked the beginning of joint research and became an important chapter in the lives of both scientists [11].

World War I had a severe impact on Röntgen's life. He donated all his savings, including his Nobel Prize money, to his country, lived extremely modestly, and traveled by train in third class. After his wife's death, he was left completely alone.

In 1923, the scientist fell ill. The doctor who examined him was struck by the modesty of the patient, whose name was known throughout the world. The irony of fate was that his diagnosis, colon cancer, was made using his own discovery, X-rays.



Fig. 5. Wilhelm Conrad Röntgen. Photograph. University of Würzburg, late XIX century (Würzburg University Library Archives, public domain)

Рис. 5. Вильгельм Конрад Рентген. Фотография. Университет Вюрцбурга, конец XIX века. (Архив библиотеки университета Вюрцбурга, общественное достояние)

On February 10, 1923, Wilhelm Conrad Röntgen passed away, never once compromising his moral principles. His will instructed that his scientific papers be burned, which was carried out [12].

The world lost one of the most hardworking, brilliant, and humane scientists, whose name is forever inscribed in history thanks to a discovery that changed the course of medicine and the fate of humanity (Fig. 5).

Do not look back — look life in the face,
Do not give up.
Lift your head, pay no heed to groans.
Whoever strives for a goal — do not retreat,
Do not look at backs and the past.
Look into the eyes of the light that lies ahead.

Richard von Volkmann. Berlin, 1890

ADDITIONAL INFORMATION

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ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

М. Ф. Сухарев, С. Б. Фицев, М. Г. Рожкова



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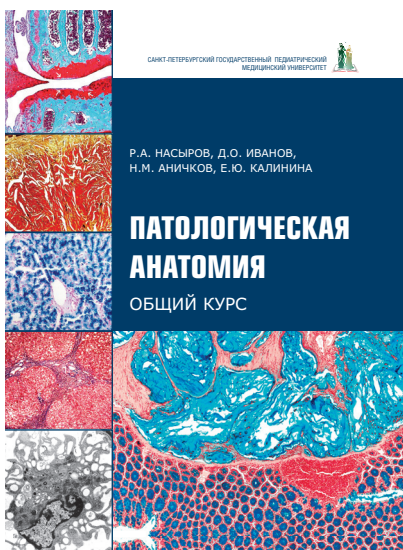
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Р.А. Насыров, Д.О. Иванов, Н.М. Аничков, Е.Ю. Калинина



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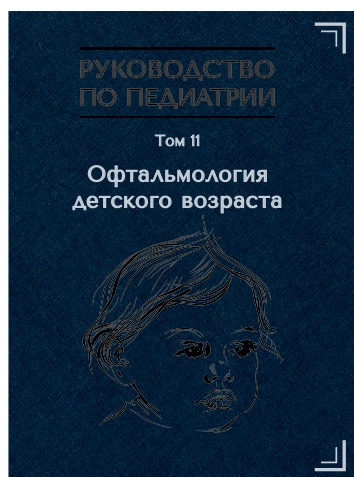
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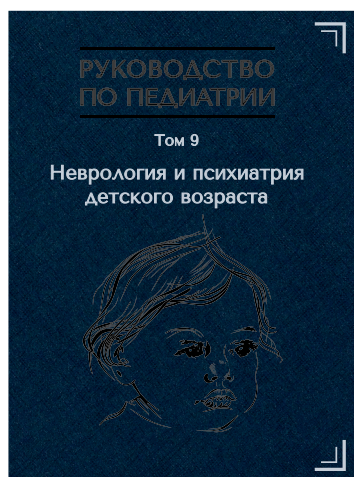
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