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ЖУРНАЛ ВКЛЮЧЕН В ПЕРЕЧЕНЬ ВАК

ДИАГНОСТИКА И ЛЕЧЕНИЕ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ИШЕМИЕЙ НИЖНИХ КОНЕЧНОСТЕЙ
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The team of the Pulmonology Department of the Federal Clinical and Research Center FMBA of Russia (Head MD. PhD Anna G. Sotnikova). 3D reconstruction of CT scans of the lungs of a patient with idiopathic pulmonary fibrosis (performed by MD, PhD I.L. Gubsky).

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Diagnostics and Treatment of Patients with Chronic Limb Ischemia (Single-Center Experience)

I.P. Mikhailov, N.V. Borovkova, B.V. Kozlovskiy, I.N. Ponomarev, G.R. Ramazanov, N.E. Kudryashova, V.A. Arustamyan, E.V. Shevchenko, L.S. Kokov, L.T. Khamidova

Sklifosovsky Research Institute of Medical Care, Moscow, Russia

ABSTRACT

BACKGROUND: *The success of treating the patients with chronic ischemia of the lower limbs consists of a number of components, such as the full-scale diagnostics; the re-vascularisation volume, the therapeutic means (including the use of modern developments in angiogenesis); the engagement of specialists from the adjacent fields.* ***AIM:*** *the improvement of treatment results in patients with chronic ischemia in the lower limbs and developing an optimal treatment and diagnostic algorithm for this group of patients.* ***METHODS:*** *The analysis included the treatment results of 218 patients with chronic ischemia of the lower limbs (136 males, 82 females; the mean age was 67±6 years), of which 144 patients were operated, 74 were treated conservatively. Diagnostics and examination methods: ultrasound angioscanning, single-photon emission computed tomography combined with three-phase scintigraphy and computed tomography, consulting by a neurologist and a cardiologist, electroneuromyography by prescription from the neurologist and additional examinations by prescription from the cardiologist. The follow-up was implemented as the control out-patient examinations or upon the repeated hospitalization. The follow-up period was 6 months.* ***RESULTS:*** *The distribution of patients by the degree of ischemia as per the classification by A.V. Pokrovsky was the following: IIA — 57 (26.1%), IIB — 31 (14.2%), III — 42 (19.2%), IV — 88 (40.5%) patients. The number of open-access surgeries conducted was 56 (25.7%), with 64 endovascular (29.4%) and 24 hybrid ones (11.0%); conservative therapy was administered to 40 patients (18.3%), conservative therapy accompanied by additional administrations of plasma-free auto-platelet lysate — 34 (15.6%). In the group of operated patients, there were no significant differences depending on the method of surgical treatment at the early post-surgery period and after 6 months of follow-up (p >0.05). Among the patients receiving conservative therapy, the best results at the follow-up of 6 months were reported in patients, in which the standard therapy was accompanied by stimulation of angiogenesis with auto-platelet factors (p <0.05). The presence of ischemic neuropathy was investigated in 98 patients. Neuropathy was detected in 69 cases using the method of electroneuromyography. After prescribing the neurotropic therapy, resolving of neuropathic pain was reported in 52 (75.4%) patients.* ***CONCLUSION:*** *The multi-disciplinary approach developed by us for the diagnostics and treatment of patients with chronic ischemia of the lower limbs, allows for improving the treatment results, while the extended spectrum of diagnostic methods allows for evaluating the risk factors, for determining the optimal treatment tactics and for objectively evaluating the dynamic changes of the patient status.*

Keywords: *chronic ischemia of the lower limbs; plasma-free lysate of autologous platelets; three-phase scintigraphy; ischemic neuropathy; re-vascularisation.*

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BACKGROUND

Chronic ischemia of the lower limbs is a socially significant disease of the XXI century. According to the data from the World Health Organization, the impairments of the arteries in the lower limbs take the third place within the structure of atherosclerotic diseases, which is 3% of the whole population worldwide [1]. Upon the progression of chronic ischemia in the lower limbs, critical ischemia in the lower limbs develops, which, in turn, in the absence of providing medical aid at the period of 6 months, can lead to amputations in 40% of cases and shows 20% mortality [2].

In the absence of indications for surgical re-vascularisation or the absence of the possibilities of its conduction, the actual issue is developing new methods of therapeutic means, primarily the use of therapeutic angiogenesis. The methods of angiogenesis were a subject of multiple research

Диагностика и лечение пациентов с хронической ишемией нижних конечностей (опыт одного центра)

И.П. Михайлов, Н.В. Боровкова, Б.В. Козловский, И.Н. Пономарёв, Г.Р. Рамазанов, Н.Е. Кудряшова, В.А. Арустамян, Е.В. Шевченко, Л.С. Коков, Л.Т. Хамидова

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АННОТАЦИЯ

Обоснование. *Успех лечения больных с хронической ишемией нижних конечностей складывается из ряда составляющих, таких как полноценная диагностика; объём реваскуляризации, терапевтических мер (в том числе применение современных разработок в области ангиогенеза); привлечение смежных специалистов.* ***Цель исследования*** *— улучшение результатов лечения пациентов с хронической ишемией нижних конечностей и разработка оптимального лечебно-диагностического алгоритма для данной группы пациентов.* ***Методы.*** *Проанализированы результаты лечения 218 пациентов с хронической ишемией нижних конечностей (136 мужчин, 82 женщины; средний возраст 67±6 лет), из них 144 пациента прооперированы, 74 — пролечены консервативно. Методы диагностики и обследования: ультразвуковое ангиосканирование, однофотонная эмиссионная компьютерная томография, совмещённая с трёхфазной сцинтиграфией и компьютерной томографией, консультирование неврологом и кардиологом, электронейромиография по назначению невролога и дополнительные обследования по назначению кардиолога. Динамику оценивали на контрольных амбулаторных осмотрах либо при повторной госпитализации. Срок наблюдения — 6 месяцев.* ***Результаты.*** *Распределение пациентов по степеням ишемии по А.В. Покровскому было следующим: IIA — 57 (26,1%), IIБ — 31 (14,2%), III — 42 (19,2%), IV — 88 (40,5%). Открытых хирургических операций выполнено 56 (25,7%), эндоваскулярных — 64 (29,4%), гибридных — 24 (11,0%); консервативное лечение получили 40 (18,3%), консервативное лечение, дополненное введением бесплазменного лизата аутотромбоцитов, — 34 (15,6%). В группе прооперированных больных значимых различий в зависимости от метода хирургического лечения в раннем послеоперационном периоде и спустя 6 месяцев наблюдения не было (p >0,05). Среди больных, получавших консервативную терапию, лучшие результаты через 6 месяцев наблюдения отмечены у пациентов, которым стандартная терапия была дополнена стимуляцией ангиогенеза аутотромбоцитарными факторами (p <0,05). На предмет ишемической нейропатии обследовано 98 пациентов. Нейропатия методом электронейромиографии выявлена в 69 случаях. После назначения нейротропной терапии купирование нейропатических болей отмечено у 52 (75,4%) пациентов.* ***Заключение.*** *Разработанный нами мультидисциплинарный подход к диагностике и лечению пациентов с хронической ишемией нижних конечностей позволяет улучшить результаты лечения, а расширенный спектр диагностических методик помогает определить факторы риска, выбрать оптимальную лечебную тактику и объективно оценить динамику состояния пациентов.*

Ключевые слова: *хроническая ишемия нижних конечностей; бесплазменный лизат аутологичных тромбоцитов; трёхфазная сцинтиграфия; ишемическая нейропатия; реваскуляризация.*

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works, with proving its efficiency in the patients with intermittent claudication and in groups of patients with minor trophic lesions [3–5]. But, even when saving the limb or when decreasing the degree of ischemia, the quality of life in a patient can be significantly decreased due to peripheral neuropathy. In case of chronic ischemia in the lower limbs, the peripheral nerves experience certain morphological reorganizations. Upon performing the reconstruction and morphological remodeling of soft tissues, the process may affect the peripheral nerve with the development of compression-ischemic neuropathy [6, 7].

Upon the modern view on the problem, it becomes evident that the success of treating patients with chronic ischemia of the lower limbs includes several components: a complex set of modern diagnostic methods; re-vascularisation of the limb, the extent of which is evaluated by a group of specialists; the

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extension of therapeutic means (including the use of developments in angiogenesis); the involvement of specialists from adjacent fields.

The research work presents an experience of treating the patients with chronic ischemia of the lower limbs according to the developed algorithm.

Research aim — improvement of treatment results in the patients with chronic ischemia of the lower limbs and developing an optimal treatment and diagnostic algorithm for this group of patients.

METHODS

Research design

Retrospective single-center observational.

Conformity Criteria

Inclusion criteria: chronic ischemia of the lower limbs; atherosclerotic origin of the disease; age from 45 to 90 years old.

Exclusion criteria: severe heart failure; acute myocardial infarction dated less than one month without the re-vascularisation of the myocardium; acute impairment of cerebral circulation dated less than one month; thromboangiitis; oncology diseases with low survival prognosis.

Research facilities

The research included patients treated at the Vascular Surgery Department of the State Budgetary Healthcare Institution "Sklifosovsky Institute for Emergency Medicine of the Healthcare Department of Moscow City" (SBHI Sklifosovsky IEM, HDM) during the period from 2022 until 2024.

Medical Procedure Description

The diagnostic algorithm included the following diagnostics methods:

- ultrasound angioscanning with measuring the ankle-brachial index: the "first line" examination method, allowing for visualizing the arterial circulation system of the lower limbs, for evaluating the blood circulation parameters and the type of plaques;
- the hybrid method (three-phase scintigraphy — single-photon emission computed tomography, combined with computed angiography, or SPECT/CT-angiography): the method allows for visualizing the arterial circulation system in the lower limbs and shows the objective data on the status of microcirculation. The three-phase scintigraphy with osteotropic radiopharmaceutical Tc^{99}-Pirfotech, unlike the transcutaneous oxymetry, provides a possibility of localizing the zones of depleted microcirculation and its extent. Upon the dynamic examination, one can observe the changes in the distribution of the radiopharmaceutical, which objectively reflects the improvement/aggravation of blood supply in the tissues [8];
- general methods of examination, such as electrocardiography, echocardiography, chest cavity X-ray, as well as ultrasound angioscanning of the brachiocephalic arteries, coronary angiography according to indications from the cardiologist — for the evaluation of risk factors in patients;
- electroneuromyography of peripheral nerves was used according to the prescription by the neurologist for the purpose of verifying the lesions of peripheral nerves with a background of impaired blood supply in the lower limbs;
- consulting by the specialists: the patients were obligatory assessed by the cardiologist and by the neurologist (the cardiologist detects and corrects the cardiac risk factors; the examination and medical supervision by the neurologist is necessary for detecting the neuropathies and prescribing medicines for their correction).

On an aggregate basis of the examinations conducted during the combined assessment with the radio-endovascular surgery specialists, a tactics of in-patient treatment was defined. It is worth noting that all the patients with chronic grade IIA ischemia in the lower limbs, as well as with chronic grade IIB ischemia of the lower limbs, in which, with a background of therapy, the degree of ischemia was decreasing, according to the recommendations [9], were not considered as candidates for surgery, also, the patients with higher degree of ischemia were considered inoperable in case of unsatisfactory status of the distal arterial circulation system or in cases of severe concomitant diseases. As for the other patients, a decision was drawn up on the extent and the type of surgical intervention: open-access reconstruction, endovascular intervention or hybrid surgery.

For the purpose of therapeutic angiogenesis, a medicinal product based on the autoplatelet pro-angiogenic factors was developed — a plasma-free lysate of autologous platelets. The application of this medicine in inoperable patients has shown satisfactory results [9, 10].

Research findings

Main research outcomes: decreased degree of ischemia, preserving the limb.

Additional criterion for operated patients: passability of the reconstructed area after a certain follow-up period; healing of wounds in cases of open-access interventions; local wound-related complications.

Additional criterion for all the patients: improvement in the distribution of the radiopharmaceutical according to the data from three-phase scintigraphy; decreased intensity of neuropathic pain.

Methods of registration of outcomes

The control procedures were arranged during the control out-patient examinations or upon the repeated hospitalization in 3 and in 6 months after treatment with implementing the whole diagnostic algorithm.

Statistical analysis

The statistical analysis of data was carried out using the STATISTICA software version 10.0. The following nonparametric methods were used: χ^2-test, Mann-Whitney test and McNemar's test. The statistically significant differences were considered the ones with $p < 0.05$.

RESULTS

Research sample (participants)

A total of 218 patients with chronic ischemia of the lower limbs were treated, of which 136 were males and 82 were females, the mean age of which was 67±6 years (Table 1). Surgical interventions were performed in 144 patients, conservative therapy was used in 74. The research included patients with chronic ischemia of the lower limbs of atherosclerotic origin with grades IIB–IV according to the classification by A.V. Pokrovsky.

Main research outcomes

In general, based on the results of combined examination and discussions on the treatment concept for the patients, three groups of surgical interventions can be isolated: open-access reconstruction, endovascular interventions and hybrid surgeries. The extent and the type of interventions were determined by the type and the level of lesions in the arteries along with the spreading of the impairment. The types of surgical interventions and the methods for therapeutic correction are provided in Fig. 1 and in Tables 2 and 3 — the results of surgical and conservative therapy used in patients, respectively.

Upon the paired comparison of the surgical groups, we did not reveal any significant differences ($p > 0.05$, Mann-Whitney U-test). Taking into consideration the small rate of amputations and mortality, these parameters were not statistically evaluated. Thus, a conclusion can be made that it is justified to choose the surgical tactics depending on the type, the location and the spreading degree of the atherosclerotic lesions in the arteries of the lower limbs.

Table 1

Clinical-demographic characterization of patients

Parameter	Patients, *n* (%)
Gender: • males • females	 136 (62.4) 82 (37.6)
Age, years	67±6
Ischemic heart disease	180 (82.6)
Hypertensive disease	192 (88.1)
Chronic kidney disease, compensation	58 (26.6)
Obesity	126 (57.8)
Chronic cardiac failure, compensation	92 (42.2)
Smoking	126 (57.8)
Degree of ischemia acc. to the Fountain–Pokrovsky: • IIA • IIB • III • IV	 57 (26.1) 31 (14.2) 42 (19.3) 88 (40.4)

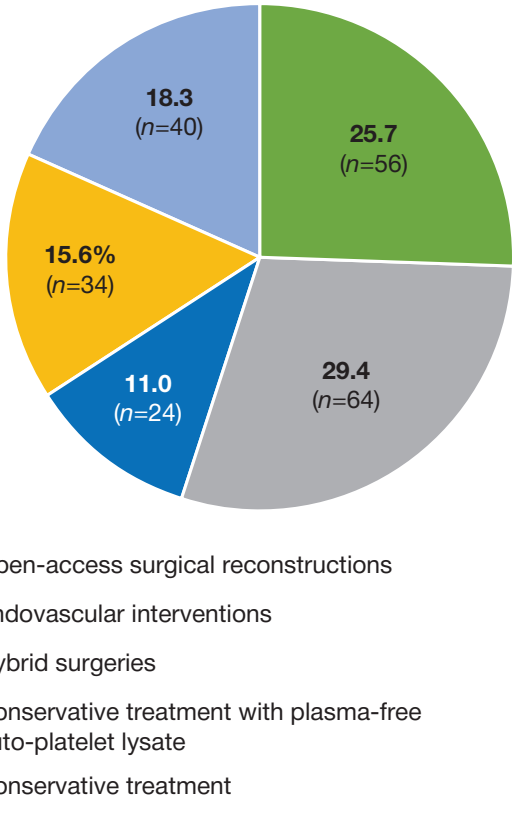

Fig. 1. The methods of treating patients with chronic ischemia of the lower limbs, %.

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Table 2

Results of surgical treatment arranged for the patients, *n*=144

Parameter	Surgical interventions, *n* (%)		
	Open-access surgery *n*=56	Endovascular *n*=64	Hybrid *n*=24
Improvement at the early time period	52 (92.8)	60 (93.8)	23 (95.8)
Passability of re-constructed areas at the 6 months' time point	48 (85.7)	53 (82.8)	20 (83.3)
Re-thromboses	8 (14.3)	11 (17.2)	4 (16.7)
Repeated surgeries	5 (8.9)	7 (10.9)	2 (8.3)
Amputations	1 (1.8)	1 (1.6)	-
Mortality	1 (1.8)	1 (1.6)	-

Table 3

Results of conservative therapy arranged for the patients, *n*=74

Parameter	Conservative *n*=40	Conservative + PFAPL *n*=34
Decreased ischemia degree within 6 months	28 (70.0)	28 (82.4)
Surgeries within 6 months due to developing indications	12 (30.0)	6 (17.7)
Amputations	2 (5)	1 (2.9)
Mortality	1 (2.5)	-

Note. PFAPL — plasma-free auto-platelet lysate.

When evaluating the results of conservative therapy, after 3 and 6 months of follow-up, we have observed better results for all the parameters in a group of patients, in which standard therapy was accompanied by stimulation of angiogenesis with autoplatelet factors (p <0.05, Mann-Whitney U-test).

The examination purposed to reveal the presence of post-ischemic and compression-ischemic neuropathies was carried out in 98 patients: signs of impaired conductivity were reported in 69 (70.4%) patients, of which 40 were operated and 29 were receiving conservative therapy, including the one with using the auto-platelet lysate. Ischemic peripheral neuropathy was diagnosed in 50 patients, mixed-type form — in 19. All the patients had received prescriptions of neurotropics from the neurologist at the out-patient phase. According to the questionnaires, the pain syndrome regressed in 52 (75.4%) patients.

Based on the satisfactory treatment results, we have developed a treatment-diagnostic algorithm for patients with chronic ischemia of the lower limbs (Fig. 2).

DISCUSSION

This article demonstrates the experience of treating the patients with chronic ischemia of the lower limbs with an extension of the range of diagnostic procedures and with the multidisciplinary approach. A wide spectrum of patients is presented in terms of the degrees of ischemia, but it is worth noting that 40.5% were the patients with chronic ischemia of the lower limbs stage IV according to the classification by A.V. Pokrovsky. This segment was the exact source of lethal outcomes and amputations, nevertheless, even in patients with critical ischemia we managed to achieve the general relatively low rates of unfavorable outcomes.

For achieving better results, for timely detection of risk factors and for improving the quality of life for the patients, we actively involve the specialists from the adjacent fields — cardiologists and neurologists.

Three-phase scintigraphy has proven itself as an irreplaceable objective method showing the status of the ischemic tissues and the dynamic changes of their status with a background of therapy [8], while performing this examinations using the hybrid-mode equipment (SPECT/CT-AG) allows for shortening the duration of the examination.

The principally new method of treating the inoperable patients or patients with intermittent claudication is the type of therapeutic angiogenesis — the use of plasma-free lysate of autologous platelets, allowing for improving the results of conservative therapy.

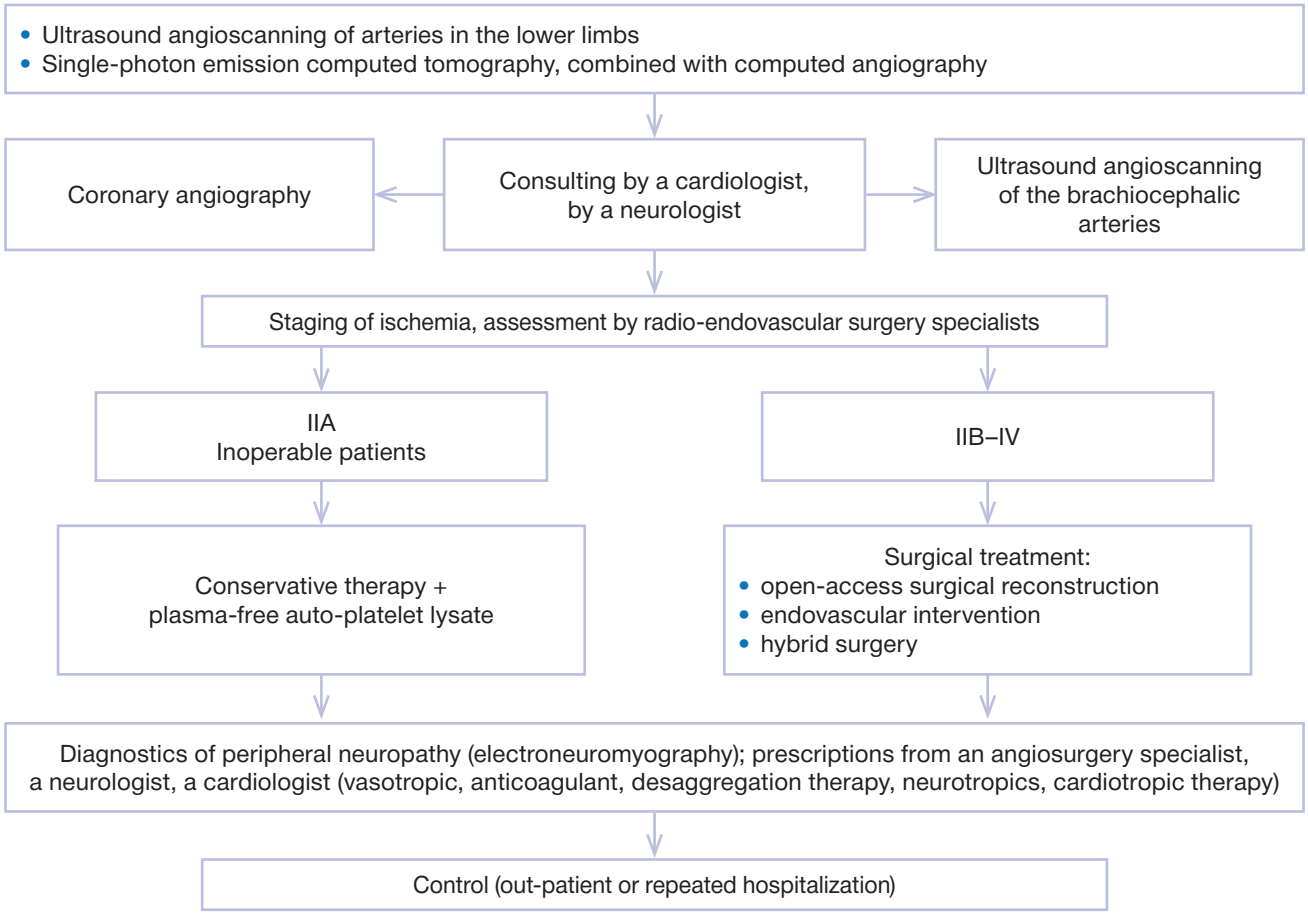

Fig. 2. Treatment-diagnostic algorithm for patients with chronic ischemia of the lower limbs.

The research included the patients with chronic ischemia of the lower limbs, meeting the inclusion criteria. Of course, the operated patients and the patients, receiving conservative therapy, represent the groups of patients that are inhomogeneous in terms of outcomes and possible complications. We did not arrange the comparison of these groups of patients between each other, for the research aim was the improvement of treatment results both in the operated and non-operated patients by selecting the optimal method for the therapy and prevention of possible complications, the most frequent of which were the early thromboses, leading to amputations, as well as the peripheral neuropathy [10].

Research limitations

The limitations of the research were the absence of separation of patients into groups by the degree of ischemia or by the level of impairment, as well as the relatively short follow-up period. The pending issue remaining is the periodicity of using the therapeutic angiogenesis, the duration of neurotropic therapy in patients with post-ischemic neuropathy and the treatment methods for operated patients with longer (over 6 months) durations, for in this case a significant increase is expected in the rates of re-thromboses and repeated surgeries.

CONCLUSION

The multi-disciplinary approach developed by us for the diagnostics and treatment of patients with chronic ischemia of the lower limbs allows for improving the treatment results. The extended spectrum of diagnostic methods allows for evaluating the risk factors and for determining the optimal treatment tactics in patients with chronic ischemia of the lower limbs, as well as for objectively evaluating the dynamic changes of their status.

ADDITIONAL INFORMATION

Author contributions. *I.P. Mikhailov*, *N.V. Borovkova*, *L.S. Kokov*, *L.T. Khamidova:* the concept and design of the study; *B.V. Kozlovskiy*, *V.A. Arustamyan*, *I.N. Ponomarev*, *N.E. Kudryashova*, *G.R. Ramazanov*, *E.V. Shevchenko*: collection and processing of material; *N.V. Borovkova*, *B.V. Kozlovskiy*,

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Data availability statement. The editorial policy regarding data sharing does not apply to this work, data can be published as open access.

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The Effectiveness of Neoadjuvant Chemotherapy Prior to Proton Beam Therapy for Head and Neck Tumors

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ABSTRACT

BACKGROUND: *Malignant tumors of the head and neck are a significant problem in modern oncology, as they occupy an important place in the structure of morbidity and mortality of the population. According to the Ministry of Health of the Russian Federation, 674,587 new cases of malignant neoplasms were registered in 2023, of which 25,038 cases were tumors of the head and neck.* ***AIM:*** *of the study was to evaluate the effect of induction drug therapy on the treatment outcomes of patients with locally advanced tumors of the head and neck who received radiation treatment using proton therapy, IMPT technique (intensity modulated proton therapy).* ***METHODS:*** *The retrospective study included an analysis of the medical records of 103 patients with head and neck tumors, who were divided into two groups: patients who received induction chemotherapy followed by proton chemoradiotherapy (n=50), and patients who did not receive induction antitumor treatment before starting proton chemoradiotherapy (n=53). T-tests for independent samples were used to assess differences between patient groups. The statistical significance of the differences was considered at a level of p <0.05.* ***RESULTS:*** *The median follow-up was 13.4 months (IQR: 11.6–21.6 months). The average follow-up time was 15.7±7.8 months. In the group of monitored patients, none interrupted planned treatment, and therapy was completed on time. In the induction chemotherapy followed by proton chemoradiation therapy group, the average OS was 27.65 months (95% CI: 24.46–30.85), while for the proton chemoradiation therapy groups it was 27.27 months (95% CI: 22.15–31.72), which was a statistically insignificant difference (Chi-squared 0.776, p=0.378). The median OS for both study groups was not reached. The progression-free survival assessment showed that the average time to progression in the induction chemotherapy followed by proton chemoradiation therapy group was 23.1 months (95% CI: 19.6–26.6), versus 21.2 months (95% CI: 16.7–25.7) in the proton chemoradiation therapy group. The incidence of grade 1 leukopenia was 30% in the induction chemotherapy followed by proton chemoradiation therapy group versus 20.8% in the proton chemoradiation therapy group, the incidence of grade 3 disorders was 26% in the induction chemotherapy followed by proton chemoradiation therapy group and 11.3% in the proton chemoradiation therapy group, and grade 3 complications were noted only in the induction chemotherapy followed by proton chemoradiation therapy group (12%). These differences are statistically significant (p <0.01).* ***CONCLUSION:*** *This study demonstrated that induction chemotherapy does not improve overall survival and progression-free survival in patients with locally advanced squamous cell carcinoma of the head and neck receiving proton chemoradiotherapy.*

Keywords: *neoadjuvant therapy, tumors of the head and neck area, proton therapy.*

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BACKGROUND

Malignant tumors of the head and neck area represent a significant problem in modern oncology, for they take an important place within the structure of the morbidity and mortality of the population. According to the data from the Ministry of Health of the Russian Federation, in 2023, a total of 674,587 new cases of malignant neoplasms were registered, of which 25,038 cases were the tumors of the head and neck area [1].

Эффективность неоадъювантной химиотерапии перед протонной лучевой терапией опухолей головы и шеи

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АННОТАЦИЯ

Обоснование. *Злокачественные опухоли головы и шеи представляют собой значимую проблему в современной онкологии, так как занимают важное место в структуре заболеваемости и смертности населения. По данным Минздрава России, в 2023 году зарегистрировано 674 587 новых случаев злокачественных новообразований, из которых 25 038 составили опухоли головы и шеи.* ***Цель исследования*** *— оценить влияние индукционной лекарственной терапии на результаты лечения пациентов с местнораспространёнными опухолями головы и шеи, получивших лучевое лечение методом протонной терапии, методикой IMPT (протонная терапия с модулированной интенсивностью).* ***Методы.*** *Ретроспективное исследование включало анализ медицинских карт 103 пациентов с опухолями головы и шеи, которые были разделены на две группы: пациенты, получавшие индукционную химиотерапию с последующим проведением протонной химиолучевой терапии (n=50), и пациенты, не получавшие индукционного противоопухолевого лечения до начала протонной химиолучевой терапии (n=53). Для оценки различий между группами пациентов применяли t-тест для независимых выборок. Статистическая значимость различий считалась при уровне p <0,05.* ***Результаты.*** *Среднее время наблюдения за пациентами составило 15,7±7,8 месяца, медиана наблюдения — 13,4 месяца (IQR 11,6–21,6). В группе отслеженных пациентов ни один не прервал планового лечения, терапия завершена в установленный срок. В группе пациентов, получивших индукционную химиотерапию с последующим проведением протонной химиолучевой терапии, средняя общая выживаемость составила 27,65 месяца (95% ДИ 24,46–30,85), тогда как для группы пациентов, не получавших индукционного противоопухолевого лечения до начала протонной химиолучевой терапии, — 27,27 месяца (95% ДИ 22,15–31,72), что являлось статистически незначительным различием (Хи-квадрат 0,776; p=0,378). Оценка выживаемости без прогрессирования показала, что среднее время до прогрессирования в группе индукционной химиотерапии с последующим проведением протонной химиолучевой терапии составило 23,1 месяца (95% ДИ 19,6–26,6) против 21,2 (95% ДИ 16,7–25,7) в группе протонной химиолучевой терапии. Частота лейкопении I степени составила 30% в группе с индукционным химиотерапевтическим лечением против 20,8% в группе без индукционной химиотерапии, частота развития нарушений III степени — 26% и 11,3% соответственно, при этом осложнения III степени были отмечены только в группе пациентов, получавших индукционную химиотерапию (12%). Данные различия являются статистически значимыми (p <0,01).* ***Заключение.*** *Индукционная химиотерапия не улучшает общую выживаемость и выживаемость без прогрессирования у пациентов с местнораспространённым плоскоклеточным раком головы и шеи, получающих протонную химиолучевую терапию.*

Ключевые слова: *неоадъювантная терапия; опухоли головы и шеи; протонная лучевая терапия.*

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Among the modern therapeutic approaches, induction chemotherapy is used as a stage before the radical radiation therapy begins in cases when the volume of the tumor masses or their spreading do not allow providing the acceptable coverage by the exposure dosage or significantly increase the risks of serious complications in the normal tissues. The main objective of induction chemotherapy in that case is the decrease of the dimensions of the tumor masses and following the dosage-volume limitations when conducting the distant radiation therapy.

As of today, according to the MACH-NC meta-analysis that included the data from 107 research works with the participation of 19,805 patients, the application of induction chemotherapy has not demonstrated a significant improvement of the overall survival in patients (HR = 0.96; 95% CI: 0.90–1.01). At the same time, simultaneous chemoradiation therapy (CRT) has shown a more significant effect, decreasing the risk of mortality by 18% (HR = 0.82; 95% CI: 0.78–0.86). These results indicate the benefit of simultaneous chemoradiation therapy before induction chemotherapy in the improvement of the overall survival of the patients [2]

In the treatment of locally spreading processes, induction chemotherapy was repeatedly compared to the combined mode of chemoradiation therapy. No conclusive evidences were revealed in terms of improving the results, and the majority of research works devoted to the role of induction therapy in the treatment of tumors of the head and neck area, were evaluating specifically the photon beam therapy, while the role of proton therapy remains uninvestigated [3].

In the worldwide literature, there are data stating that proton irradiation suppresses the expression of factors, lympho-, angiogenesis and immune tolerance, facilitating the survival of less aggressive clones of tumor population, but their effects on the tumor biology remains poorly investigated [4, 5]. Because the efficiency of proton therapy is confirmed by our own clinical observations, there remains an interest to the improvement of long-term efficiency results by means of intensifying the anti-tumor medication therapy [6].

Research aim: The main aim of the research was to conduct a comparative analysis of two groups by key clinical outcomes, including the overall survival (OS) and progression-free survival (PFS), as well as to determine the effects of induction chemotherapy on the hematological toxicity.

METHODS

Research design

This retrospective research included an analysis of medical records from 103 patients with tumors in the head and neck area, which were divided into two groups: the patients receiving induction chemotherapy with further conduction of proton chemoradiation therapy (IPCRT) (n=50), and the patients not receiving induction antitumor therapy before the initiation of proton chemoradiation therapy (PCRT) (n=53).

For checking the conformity of the distribution of the quantitative variables to the normal one in each of the groups, the Shapiro-Wilk test was used. Despite the deviation from the normal distribution when evaluating the dosages of applied radiation therapy, taking into consideration the range of clinically recommended dosages, the analysis was carried out using the t-test for independent samples. Statistical significance of differences was considered in cases of p being < 0.05.

Conformity Criteria

The retrospective research was enlisting the patients with morphologically confirmed squamous cell cancer of the oropharynx or of the oral cavity, the locally spreading stage of the disease (III–IVb), the absence of signs of remote metastatic activity (M0), the absence of previously conducted radiation therapy and the satisfactory functional status — ECOG 0-1.

Research facilities and duration

From January 2019 until December 2024, proton beam therapy sessions were arranged with the use of ProteusPlus235 proton-cyclotron complex within the premises of the Federal State Budgetary Institution “Federal Scientific and Clinical Center of Medical Radiology and Oncology” under the Russian Federal Medical-Biological Agency in a total of 4,049 patients. The selection of patients was carried out using the “Protoregistr-2021” database, developed and registered within the framework of the state assignment from the Russian Federal Medical-Biological Agency [7].

Ethical review

All the research participants have signed the voluntary informed consent for treatment. The authors claim that the approval from the Ethics committee was not required, for the retrospectively analyzed data were based on the anonymized data and the treatment was conducted in accordance with the clinical recommendations from the Ministry of Health of the Russian Federation.

Medical procedure description

The patients were receiving a cycle of proton therapy following the mode of five-days fractioning with a single dosage (SD) of 2Gr to the total dosages (TD) of 50–60Gr applied to the zones of local-regional lymphatic collector and with the total dosage of 66–70Gr applied to the area of the primary tumor focus and the high risk zones. As an induction medication therapy, the patients were receiving the DCF scheme of not less than 2 cycles (Docetaxel-Cisplatin-Fluorouracil with a 21 days cycle) with further evaluation of the dynamic changes and, in the absence of signs of progression, with the conduction of proton chemoradiation therapy.

The dosimetric planning of proton therapy was carried out using the Phillips Pinnacle 3 planning system for the treatment conducted using the ProteusPlus235 apparatus with the Pencil Beam Scanning methods.

All the patient cases were discussed during the multi-disciplinary consilium, where decisions were made on the management tactics. The detailed characteristics are summarized in table 1. The test groups were comparable by the key clinical characteristics. A demonstration of the differences between proton and photon therapy plans in the dosimetric distribution is shown in Fig.1.

Statistical analysis

The median of follow-up was 13.4 months (IQR: 11.6–21.6 months). The mean follow-up time for the patients was 15.7±7.8 months. In the group of tracked patients, no one has interrupted the scheduled treatment, the therapy was completed at the pre-defined time. For the evaluation of the differences between the groups of patients, t-tests were used for independent samples. The statistical significance of differences was the p level being < 0.05.

Table 1

Comparative and quantitative characteristics of the test groups of patients

Parameter	IPCRT (n=50)	PCRT (n=53)	Comparability (p-value)
Gender, *n* (%)			
• M	36 (72)	35 (66)	0.513
• F	14 (28)	18 (34)	
Age (mean ± SD)	55.9±10.2	55.3±11.9	0.804
Tumor stage			
• 2	12	16	0.772
• 3	16	15	
• 4	22	22	
N-stage			
• 1	38	33	0.142
• 2	7	16	
• 3	5	4	
AJCC stage (TNM)			
• III	27 (54)	25 (52.1)	0.849
• IV	23 (46)	23 (47.9)	
Total focal dosage			
• High risk	66.2±2.1	65.8±2.4	0.761
• Mid risk	54.0±3.4	53.7±3.2	0.638
• Low risk	50.5±2.9	50.2±2.7	0.078
CRT type			
• Cisplatin	25 (50)	28 (52.8)	0.928
• Carboplatin	25 (50)	25 (47.2)	
Topographic group			
• The oropharynx	30 (60)	28 (52.8)	0.593
• The oral cavity	20 (40)	25 (47.2)	

Note. IPCRT — induction chemotherapy with further conduction of proton chemoradiation therapy, PCRT — proton chemoradiation therapy.

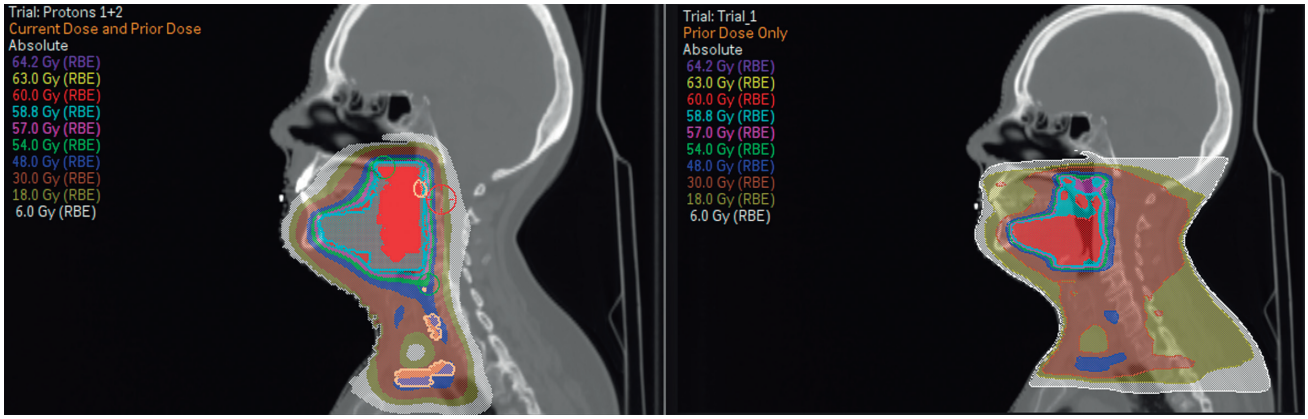

Fig. 1. Dosimetry differences in the plans of proton (on the left side) and photon (on the right side) radiation therapy.

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RESULTS

Research sample (participants) and primary findings

The first stage included the analysis of the parameters of overall survival in the test groups of patients using the Kaplan-Meier curves (Fig. 2). In the group of patients receiving induction chemotherapy, the mean OS was 27.65 months (95% CI: 24.46 – 30.85), while in the group without induction chemotherapy — 27.27 months (95% CI: 22.15–31.72), which was a statistically insignificant difference (Chi-square = 0.776, p=0.378). The median OS for both test groups was not achieved due to the limited duration of following-up the patients.

The evaluation of the progression-free survival rate has shown that the mean time to progression in the group of induction chemotherapy was 23.1 months (95% CI: 19.6–26.6), versus 21.2 months (95% CI: 16.7–25.7) in the group where the treatment did not include the induction. The median time to progression was the following: the group with the induction type of chemotherapy — 26.3 months (95% CI: 18.7– 33.8), the group without the induction mode — 18.8 months (95% CI: 8.0–29.6). Despite the fact that the median PFS was higher in the group with induction chemotherapy, no statistically significant differences were detected between the groups (Chi-square = 0.293, p=0.589) (Fig. 3).

None of the analyzed factors (stage of the disease, test group, HPV-status, age, type of the used antitumor medication) had a significant statistical effect on our patient sample.

Evaluations were also carried out for the rate and the degree of developing leucopenia: as expected, the group of induction medication therapy demonstrates the higher rate and degree of hematological abnormalities (table 2).

The rate of grade 1 leucopenia was 30% in a group of patients, receiving induction chemotherapy with further proton chemoradiation therapy, versus 20.8% in a group of patients not receiving induction antitumor therapy before the initiation of proton chemoradiation therapy, the rate of developing grade 3 disorders was 26% in the group of induction chemotherapy and 11.3% in the group without the induction, while grade 3 complications were reported only in the group of patients receiving induction chemotherapy (12%). These differences are statistically significant (p <0.01) and confirm that induction chemotherapy increases the rate and the degree of leucopenia severity.

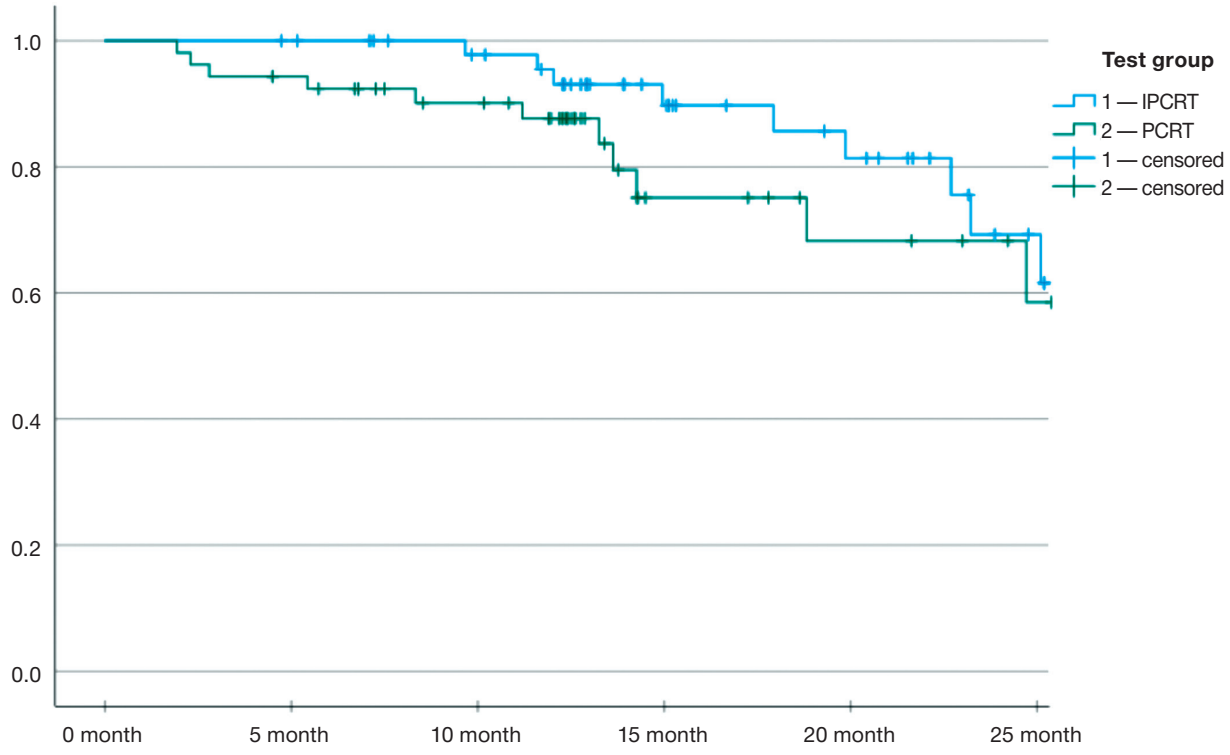

Fig. 2. Overall survival graph for the patients of the test groups using the Kaplan-Meier method. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

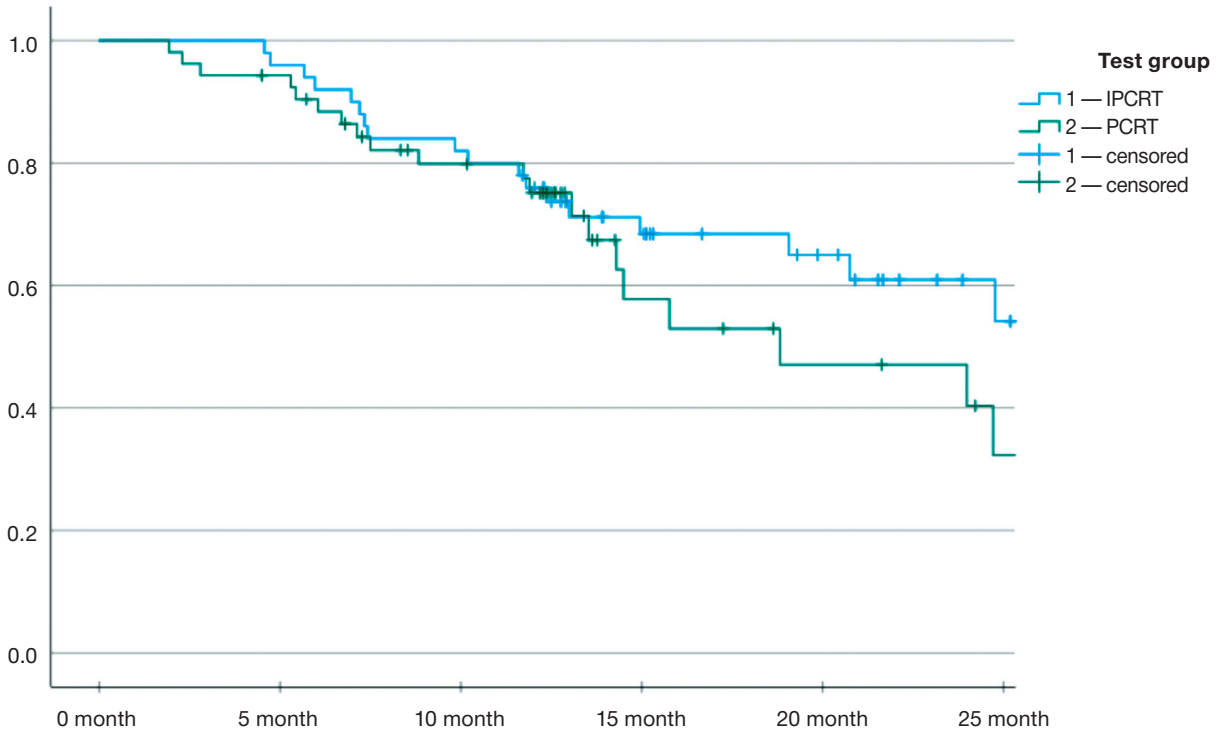

Fig. 3. Progression-free survival rate graph for the test groups — Kaplan-Meier's method. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

Table 2

Assessment of the degree of leucopenia development

Group	Leucopenia degree								Total, *n*
	0	%	1	%	2	%	3	%	
IPCRT	16	32.0	15	30.0	13	26.0	6	12.0	50
PCRT	36	67.9	11	20.8	6	11.3	0	0.0	53
Total	52	-	26	-	19	-	6	-	103

Note. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

DISCUSSION

Our research has demonstrated that induction chemotherapy does not improve overall survival and progression-free survival in patients with locally spreading squamous cell cancer of the head and neck area, receiving proton chemoradiation therapy. However, the presence of induction therapy is associated with the higher rate of hematological disorders, which evidently leads to interrupting the treatment, to the usage of additional resources, as well as to the elevation on the risks of complications. Thus, such an approach should not be used in the routine practice. These data confirm the tendency observed in the publications worldwide, now transferred to the group of proton therapy.

The research had a number of limitations, primarily, due to its relatively small sample size (n=103), which may limit the statistical power of analysis. Also, the follow-up period was lasting at an average of 15.7 months, which may be insufficient for the evaluation of long-term treatment effects.

CONCLUSION

The routine usage of induction chemotherapy before proton chemoradiation therapy does not provide significant benefits in terms of overall survival and progression-free survival rates. Additional factors, having a potential effect on the patients' survival rate and treatment tolerability, include the local toxicity, the volume of the tumor masses and the fractioning modes, which represent a subject for our further research.

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ADDITIONAL INFORMATION

Author contributions. *Yu.D. Udalov*: the concept and design of the study; *A.V. Nezvetsky*, *I.V. Nezvetskaya*: material processing, data analysis, writing and editing of the text. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Automated Morphometry of the Prostate Gland by the Results of Magnetic Resonance Imaging

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ABSTRACT

BACKGROUND: *Within the framework of the experiment on using the innovative technologies in the field of computer vision for analyzing the medical images and on further usage of these technologies in the healthcare system of the City of Moscow, the research was carried out using the equipment based on the artificial intelligence (AI-service) for the purpose of automatization of the morphometry of the prostate gland using the magnetic resonance imaging (MRI), for the issue is topical due to the high incidence of urological diseases among men. Unlike the 11 previous systems, oriented at the retrospective analysis, this solution helps the radiologists in shortening the time of describing the examination results and in increasing their accuracy.* ***AIM:*** *to evaluate the quality and the validity of automatic morphometry of the prostate gland by the MRI results using the technologies of artificial intelligence in the settings of practical healthcare.* ***METHODS:*** *A prospective diagnostic research in accordance with the methodology of reporting results of scientific research involving the STARD 2015 diagnostic tests was conducted during the period from April until October of 2024. A total of 560 MRI results were used and compared to the data from the morphometric AI-service.* ***RESULTS:*** *An evaluation of the accuracy of using the AI-service for the morphometry of the prostate gland was carried out. A total of 7 clinical monitoring procedures were conducted using 560 MRI datasets with the complete conformity reported in 71.6%. The rate of false-negative cases was 3.9%, technical defects were found in 3.8% of the cases. The integral clinical evaluation has achieved the range of 88.0–97.0%, confirming the high diagnostic quality. The predominant errors were the ones related to the contouring of the gland (52%) and incorrect measurements (13%), often related to the prolapsing of the prostate gland apex.* ***CONCLUSION:*** *The automatization of routine measurements greatly contributes to the standardizing the processes of describing the results obtained by radio-diagnostic methods. This aspect is of special importance from the point of view of providing the continuity of medical aid in case of patients presenting to various medical organizations. The artificial intelligence technologies for the automatization of the prostate gland measurements have demonstrated high clinical value in 92.0%, which indicates their accuracy and quality. These data can be used for developing new MRI-based automated morphometry products.*

Keywords: *artificial intelligence; prostate gland; morphometry; magnetic resonance imaging; MRI; radiology; diagnostic accuracy.*

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BACKGROUND

In recent years, an unswerving growth is observed in the interest to using the artificial intelligence technologies (AI) in healthcare in general and in the radiodiagnostics in particular [1–6]. The automated analysis of the results of diagnostic examinations is considered a potentially effective tool for increasing the productiveness and the quality of operations performed by radiologists, for optimizing the processes in the radiodiagnostics departments along with solving the issues of staff shortage. Constant growth is observed in the number of scientific publications on the AI topic,

Автоматизированная морфометрия предстательной железы по данным магнитно-резонансной томографии

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АННОТАЦИЯ

Обоснование. *В рамках внедрения инновационных технологий в области компьютерного зрения для анализа медицинских изображений и дальнейшего применения этих технологий в системе здравоохранения города Москвы проведено исследование инструмента на основе искусственного интеллекта (ИИ-сервис) для автоматизации морфометрии предстательной железы по магнитно-резонансным томограммам (МРТ). В отличие от 11 предыдущих систем, ориентированных на ретроспективный анализ, данное решение помогает рентгенологам сократить время описания исследований и повысить их точность.* ***Цель исследования*** *— оценить качество и достоверность автоматической морфометрии предстательной железы на результатах МРТ с помощью технологий искусственного интеллекта в условиях практического здравоохранения.* ***Методы.*** *Проспективное диагностическое исследование в соответствии с методологией репортирования результатов научных исследований диагностических тестов STARD 2015 проведено в период с апреля по октябрь 2024 года. Использованы 560 результатов МРТ, сопоставленных с данными морфометрического ИИ-сервиса.* ***Результаты.*** *Оценена точность ИИ-сервиса для морфометрии предстательной железы. Проведено 7 клинических мониторингов на 560 МРТ с полным соответствием в 71,6%. Ложноотрицательные случаи составили 3,9%, технические дефекты — 3,8%. Интегральная клиническая оценка достигла 88,0–97,0%, подтверждая высокое качество диагностики. Преобладали ошибки в оконтуривании железы (52%) и неправильные измерения (13%), часто связанные с пролабированием верхушки предстательной железы.* ***Заключение.*** *Автоматизация рутинных измерений вносит существенный вклад в стандартизацию процессов описания результатов лучевых методов исследований. Особо важен этот аспект с точки зрения обеспечения преемственности медицинской помощи при обращении пациента в различные медицинские организации. Технологии искусственного интеллекта для автоматизации измерений предстательной железы показали высокую клиническую оценку в 92,0%, что свидетельствует об их точности и качестве. Эти данные могут быть использованы для разработки новых продуктов автоматизированной морфометрии на основе МРТ.*

Ключевые слова: *искусственный интеллект; предстательная железа; морфометрия; магнитно-резонансная томография; МРТ; лучевая диагностика; диагностическая точность.*

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however, the number of scientific research products does not mean their quality, both in terms of the publications themselves and in terms of the proposed AI-based decisions. The vast majority of the published developments still includes experimental prototypes, while their underlying mathematical models were taught and tested using limited data samples. The retrospective assessment is predominant in assessing the accuracy of AI-technologies in laboratory settings, while the quantity of clinical research works with proper AI quality and applicability are vanishingly small. In the 21st century, it is difficult to believe in the

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situation, when a novel drug substance is tested only in a laboratory, not being tested in a full-scale clinical research. In terms of the AI- technologies, exactly this pattern is observed, which is completely unacceptable for modern medical sciences.

In Russia, from the year of 2020, an experiment is carried out on using the innovative technologies in computer vision for analyzing medical images and further use of these technologies in the healthcare system of the City of Moscow (hereinafter — the Moscow experiment; mosmed.ai) [7]. Currently, this is the world's largest scientific prospective multicenter research on the applicability, safety and quality of AI. Within the frameworks of the Moscow experiment, a two-staged research is conducted on using the AI-based software (the so-called AI-services), developed for solving strictly specific diagnostic tasks. The first retrospective stage involves quite a standard testing using the reference data sets, however, the second (the main) and the prospective stages included the evaluation of the quality and the stability of AI-services when operating with the real flow of examination results in the settings of practical healthcare [8–10]. Due to the long-term (lasting months and years) use of AI-technologies in real-time practice, a possibility arouses for studying their effects on the working processes in radiodiagnostics, moreover — not in general, but in a context of solving a strictly specific working operation and clinical task. One of such quite specific tasks is the morphometry of the dimensions and the volume of the prostate gland when interpreting and describing the results of magnetic resonance imaging (MRI) of the lesser pelvis. It should be noted that, within the structure of the urological diseases in men, oncological and inflammatory diseases of the prostate gland prevail, which makes their screening and diagnostics an exceptionally topical issue [11, 12].

Morphometry represents a routine procedure, which takes the working time of the radiologist and creates potential risks due to the subjectiveness of measurements. Its is evident that, for increasing the productivity and the quality of work, this procedure can be easily automated. For exactly the automatization of measurements has shown a significant shortening of the duration of describing the results of radiology examinations along with the parallel increase in the productivity of the operations performed by the radiologist [13]. It is worth noting that previously, a set of data was compiled — the "MosMedData MRI of the lesser pelvis with morphometry parameters of the prostate gland" for the purpose of calibration testing, representing a structurized set of two hundred de-personalized results of multi-parametric magnetic-resonance imaging examinations data among adult men with the presence of morphometry marks (vertical, anterior-posterior and frontal dimensions of the prostate gland in millimeters relative to axis of the organ)[1]. The images are provided in the DICOM 3.0 format, with the marking provided as the XLSX file.

With a background of the colossal interest in using AI in radiodiagnostics, the challenges of automated analysis of the results of the lesser pelvis MRI are practically not researched. In particular, not so long ago, approximately 11 AI-based developments were published for analyzing the results of the prostate gland MRI. None of them is intended for direct helping the physician by means of the automatization of the routine mechanical procedure of measuring the target organ, though the developers are trying, mainly with no success, to solve the hardest challenges of differential diagnostics. Another substantial defect is that all these developments were tested only retrospectively or in the contest mode (competing with each other), i.e. the verification and evaluation of accuracy in the real clinical settings were not implemented [14, 15].

Research aim — to evaluate the quality and the validity of automatic morphometry of the prostate gland based on the magnetic resonance imaging results using the artificial intelligence technologies in the settings of practical healthcare.

METHODS

Research design

This was a prospective diagnostic research conducted in accordance with the methodology of reporting the results of scientific research with using the STARD 2015 diagnostic tests[2].

Conformity criteria

Inclusion criteria: male patients older than 18 years; MRI scanning performed in the out-patient settings following the standard protocol; scanning protocol: loc (locators), T2-WI (T2-weighted images), T1-WI

[1] Certificate of data base registration — RU 2025620045/09.01.2025. Application No. 2024626323 dated 20.12.2024. Vasilyev Yu.A., Nasibyan N.M., Vladzimirskiy A.V. et. al. MosMedData: MRI of lesser pelvis with the morphometry parameters of the prostate gland. EDN: IXRMQR

[2] Certificate of registration of PC software — RU 2025610804/14.01.2025. Application No. 2024691653 dated 20.12.2024. Vasilyev Yu.A., Vladzimirskiy A.V., Omelyanskaya O.V. et al. Data set preparation platform. EDN: TZQQHN

(T1-weighted images), DWI (diffusion-weighted images) with fat tissue suppression and with computing the ADC (apparent diffusion coefficient) charts along with dynamic contrast enhancement (DCE); the presence of the results of automated analysis (operation of the AI-service); the presence of informed voluntary consent for conducting the research.

Exclusion criteria: motor artifacts, artifacts from foreign objects at the investigated level; technical defects of MRI-scanning; technical defects in the results of AI-service operation.

Research facilities

The examination was carried out within the premises of the State Budgetary Healthcare Institution "Scientific-Practical Clinical Center for Diagnostics and Telemedicine of the Moscow Healthcare Department" (SBHI SPCC D&T, MHD). The research was carried out with using the results of radio-diagnostic examinations, conducted at the medical organizations of the Healthcare Department of the City of Moscow, providing medical aid to adult population in the out-patient settings (municipal polyclinics). The examination results were stored at the centralized archive of medical images of the City of Moscow (the Unified Radiology Information Service of the Unified Medical Information-Analytical System of the City of Moscow, URIS of UMIAS), while their description and compilation of protocols were conducted by radiology physicians of the reference-center within the premises of the SBHI SPCC D&T (Moscow Healthcare Department).

In accordance with the Decree issued by the Moscow Government on November 21, 2019 No.1543-PP[3], SBHI SPCC D&T (MHD) is an operator of the experiment on using the innovative technologies in the field of computer vision for analyzing the medical images and further using these technologies in the Healthcare system of the City of Moscow (the Moscow experiment). The staff of the institution were performing the independent testing and quality control of the operation of the software products based on AI technologies. The developers and the right holders of the said software products are the third parties — the companies and enterprises of various form of incorporation, not affiliated by the SPCC D&T (MHD).

[3] Decree issued by the Moscow Government on November 21, 2019 No.1543-PP «On the conduction of the experiment on using the innovative technologies in the field of computer vision for analyzing the medical images and their further use in the Healthcare System of the City of Moscow». Access mode: https://www.garant.ru/products/ipo/prime/doc/73059396/

Research duration

The research work was arranged during the period from 01.04.2024 until 31.10.2024. Within the stated period of time, the tested software product based on AI-technologies was analyzing the results of MRI-scanning of the target area in accordance with the Moscow experiment procedures. A monthly sample was compiled for monitoring the operational quality (see below for detailed description of this procedure). The summarization and the analysis of the results were conducted during the period from 01.01.2025 until 01.03.2025.

Research description

An evaluation was carried out of the applicability of AI technologies for the automatization of the prostate gland measurements in the settings of practical healthcare.

The Index-test (the test method) — is a software product based on AI technologies (AI-service) for the recognition and analysis of MRI-scans of the prostate gland, integrated into the URIS UMIAS in accordance with the procedures of the Moscow experiment.

The functions of the AI-service are the following: measuring the vertical, the anterior-posterior (sagittal) and the frontal (transverse) dimensions of the prostate gland in millimeters relative to the axis of the organ (urethra); calculation of the prostate gland volume [16]. The research includes the IMV PIRADS AI-service ("Imvision" LLC, Russia) — the only participant of the Moscow experiment in the stated field (the limitations of this research shall be provided in the corresponding section at the end of the article).

Reference test: clinical monitoring of the quality of AI-service operation in accordance with the original methods, developed and validated within the settings of the Moscow experiment [14, 17, 18].

Methods of arranging the clinical monitoring of the quality of AI operation. Compilation of the sample from the whole volume of MRI-scans analyzed by the AI-service for the report period. The sample is to be compiled randomly, while its size is pre-justified and equals 80 scans every month [1]. The sample is reviewed by two radiologists with a work experience of not less than 5 years.

Each expert evaluates the results of automated analysis of this examination by two criteria: the correctness of detecting and labeling the location of the pathological signs (labeling by AI-service); the correctness of AI-service interpretation of the results of radiology examination (conclusion from the AI-service).

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Taking into consideration the morphometric characteristics of the tested AI-service, the first criterion was considered the correctness of segmentation, while the second was the measuring of the volume and size of the prostate gland. For each examination result, the expert was setting the variant of assessment: full conformity (1 point), incorrect assessment (0.5 points), false-positive result (0.25 points), false-negative result (0 points). The assessment variant was defined for each of the abovementioned criteria separately, then all the obtained points were summed; the maximum possible value of the sum for this sample was taken as 100.0%, after which the specific weight was calculated for the added sum of points; eventually, the level of clinical assessment was obtained, varying within a range from 0.0 to 100.0%.

In this context, the following approaches were used: the false-positive result means erroneous measuring of the dimensions or the volume of the prostate gland, resulting in the definition of the case as the pathological with initially normal status of the target organ; false-negative result — erroneous measurement of the dimensions or the volume of the prostate gland, resulting in the definition of the case as normal with the actual presence of pathological changes. Erroneous measurements can be due to incorrect segmentation or due to the defects of mathematical calculation, related to the classification of the results of automated analysis. An incorrect assessment means the presence of discrepancies in the measurements conducted by the AI-service and by the radiologist, however, such discrepancies are not resulting in the occurrence of false-positive or false-negative result.

The sample from the second stage included the results of clinical monitoring sessions, conducted within 7 months (each month, a new sample consisting of 80 results of the prostate gland MRI, processed by the morphometry AI-service, was compiled for monitoring purposes). Respectively, the whole research included 560 cases.

Statistical analysis

The research had not established comparison groups, due to which, the sample size was not calculated. At the same time, the sample size for the regular monitoring of the quality of AI operation is 80 scans each month. The approaches for its determination were published previously [19].

The MedCalc v. 23.1.1 statistical software (MedCalc Software Ltd, Belgium) was used during the research. No special statistical criteria were used, only the descriptive statistics procedures were applied.

RESULTS

Research sample (participants)

In the settings of practical healthcare, an evaluation was carried out of the diagnostic accuracy of the AI-service for the morphometry of the prostate gland. Using this software product in accordance with methodology of the Moscow experiment, a total of seven clinical monitoring sessions were carried out (one monitoring each month, sample size — 80 cases). As appropriate, samples of examination results were compiled, allowing for evaluating the diagnostic accuracy of the operation of AI technologies in the prospective design, i.e. in the settings of practical healthcare. For the monitoring purposes, a total of 560 prostate gland MRI results with the results of automated analysis were selected randomly.

Primary findings

The full conformity of the results of AI-service operation was obtained in 71.6% (*n*=401) of the cases (Table 1). Quite high was the percentage of cases with partial agreement with the expert physician — 20.5% (*n*=115). The specific weight of false-negative cases was 3.8% (*n*=22). Notably, almost the same level was shown for the percentage of technical defects occurring during the processing of MRI-scanning results — 3.8%, i.e. in a total of 21 cases, the AI-service was shown as technically unreliable.

Table 1

The parameters of clinical monitoring the of AI-service operation in the morphometry of the prostate gland based on the results of magnetic resonance imaging

Number (*n*=560)	Evaluation				
	Full conformity	Incorrect assessment	FP	FN	Defect
Abs.	401	115	1	22	21
%	71.6	20.5	0.2	3.9	3.8

Note. FP — false-positive result; FN — false-negative result.

The clinical assessment was conducted each month for the sample of 80 examination results, while its values varied within a range from 88.0 to 97.0%. For the total sample of 560 scanning results, i.e. for the whole period of using the AI-service in the settings of practical healthcare, the clinical assessment parameter value was 92.0%.

Separate analysis is required for the episodes of incorrect operation of the AI-service. In total, 138 results of automated analysis were to one degree or another assessed as low-quality (Fig. 1). Within the structure of the erroneous or incorrect operations of the AI-service, detected during the monitoring, the incorrect delineation of the prostate gland was prevailing — 52.0%; in 14.0% of the incorrect cases, the segmentation of one of the projections was missing. What calls attention to itself is the high percentage of incorrect measurements (including the incorrect arithmetic calculation of the volume) with a background of completely adequate segmentation of the target organ — 13.0%.

The most typical segmentation errors were related to the presence of prolapsing apex of the prostate gland in the urinary bladder, to the contouring of the gland with capturing the dilated venous plexuses or the seminal vesicles. The examples of automated analysis performed by the AI-service for the morphometry of the prostate gland by the MRI results are provided in Fig. 2 and 3.

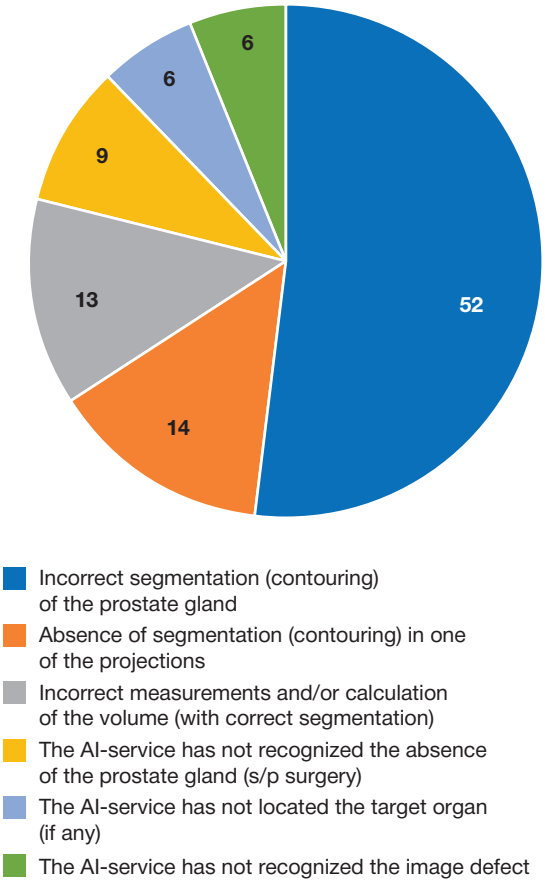

Fig. 1. The structure of incorrect or erroneous operation of the AI-service during the morphometry of the prostate gland on the results of magnetic resonance imaging, %.

The obtained data show quite high diagnostic quality of the tested tool. Hence, the AI technology (computer vision) can be considered applicable for the automatization of the prostate gland measurements.

DISCUSSION

The problematics of using AI technologies for analyzing the results of the MRI of the lesser pelvis (in particular, of the prostate gland) in scientific literature is enlightened to a certain degree unidirectionally [20–22]. General compilation is provided for the possible tasks for development in the corresponding topical area, the number of which includes the segmentation and the search for pathological foci, the classification and increasing the quality of multiparametric imaging, the detection and the differential diagnostics of malignant neoplasms, the classification of risk degree by the Gleason score[4] [23–25]. In the real development, the prevailing are the oncological diagnostics, the use of radiomics methods, as well as the multimodal approach expressed as the combined use of the MRI results and the pathomorphological examination of the prostate gland [26]. Specifically, the radiomics models have shown a high accuracy of differential diagnostics for the foci in the prostate gland. The fact that increases the value of such publications is that the developed models also pass the external validation, i.e. the independent verification via a set of new data. The meta-analysis summarizing the data from 43 articles (9983 patients) has allowed for obtaining the mean accuracy values (area under the characteristic curve) of the radiomic models — 0.91–0.93 [27], at the same time, there are still disputable issues of the precision of the results obtained when using such models, their applicability not in the laboratory, but in clinical settings. With this background, the tasks of the prostate gland morphometry have undeservedly little attention. Meanwhile, performing the routine measuring procedures by the radiology physician “manually” leads to wasting time and can always result in errors in terms of accuracy and precision [28–32].

[4] Certificate of state registration of database No. 2024620575 dated 06.02.2024. Application No. 2024620252/26.01.2024. Vasilyev Yu.A., Blokhin I.A., Geleje P.B. et al. A set of biparametric MRI data of the prostate gland with histological verification. EDN: XEAAGM. Access mode: https://telemedai.ru/nauka/nauchnaya-infrastruktura/nauchnaya-deyatelnost/intellektualnaya-sobstvennost

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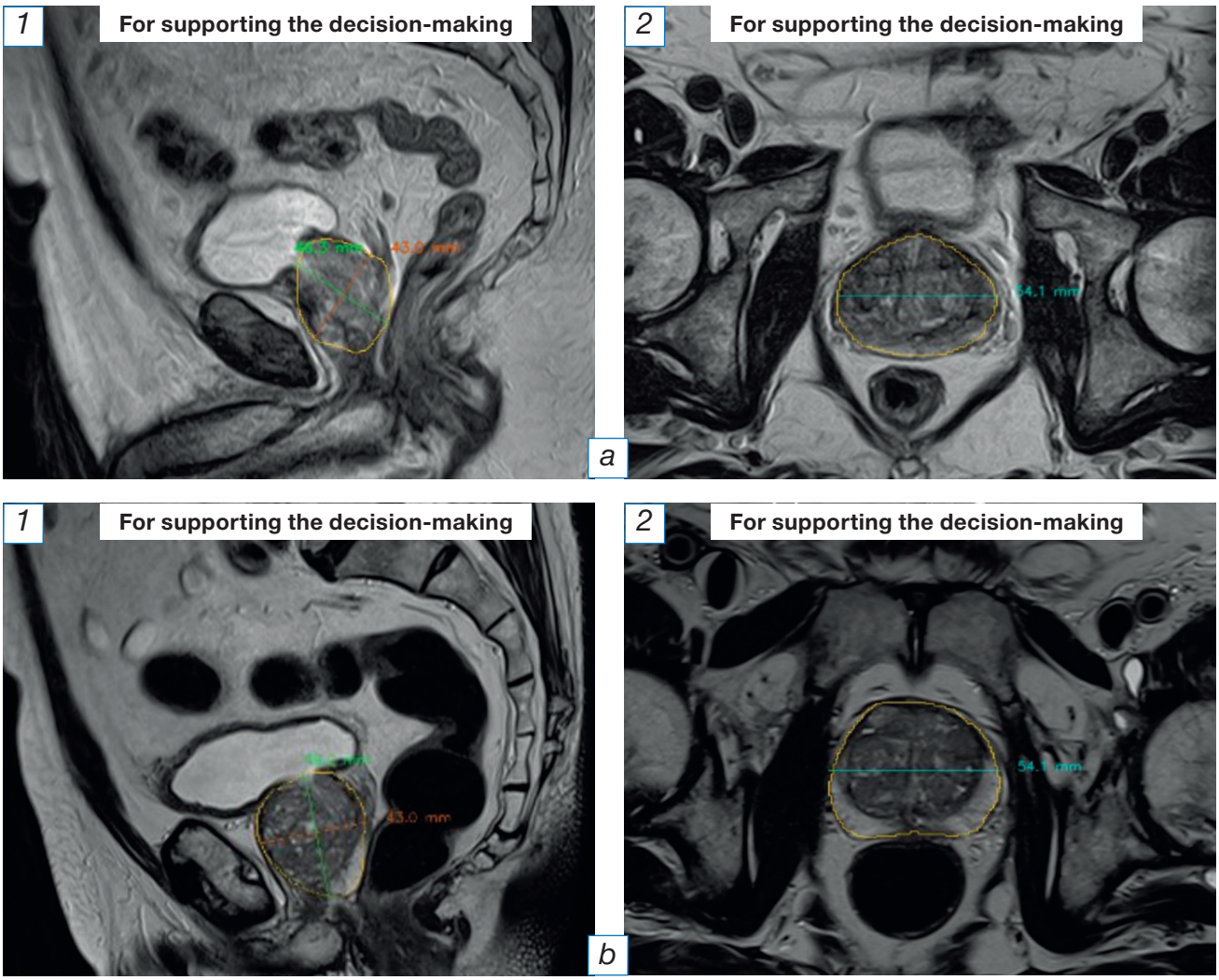

Fig. 2. The results of magnetic resonance imaging of the lesser pelvis organs in males aged 65 (*a*) and 67 (*b*) years, analyzed by the AI-service: segmentation and morphometry of the prostate gland were done correctly. *1* — sagittal projection; *2* — axial projection.

In general, the scientific literature shows a sufficiently high level of diagnostic precision of the AI (based on the typical neural network architectures) when analyzing the MRI of the prostate gland. Thus, upon the automated segmentation of the prostate gland, the Dice coefficient ranges within 0.86–0.9 [33, 34], upon the classification of the pathological manifestations, the area under the characteristic curve also reaches 0.84–0.91 [35, 36]. The accuracy of detecting the pathological foci is lower and falls within a range of 0.64–0.81 [37]. During the comparative research, it was found that AI has surpassed the international group of radiologists (consisting of 62 specialists) in terms of detecting the clinically significant prostate cancer and its classification using the PI-RADS scale (Prostate Imaging Reporting and Data System) [38]. The significant downside of these research works is their experimental pattern. All the

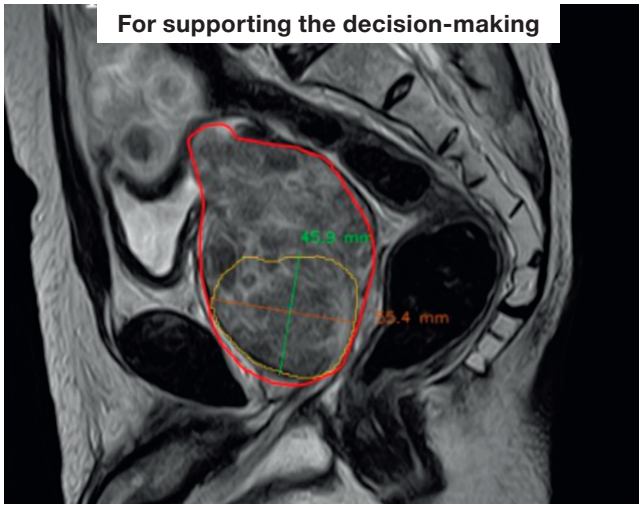

Fig. 3. The results of magnetic resonance imaging of the lesser pelvis organs in a male aged 86 years, analyzed using the AI-service: an example of incorrect segmentation of the prostate gland (the contour of the prostate gland in the sagittal projection is not marked in full range).

AI-related research on diagnostics of abnormalities in the prostate gland were conducted in laboratory settings, using the reference data sets (including the quite vast comparison of accuracy between the AI and the group of 62 physicians). Moreover, the independent analysis of the quality of such articles has shown that 47.0% of them were lacking the full and correct description of the reference data set, i.e. of the main AI accuracy measuring tool. Even more negative is the fact that up to 92.0% articles contained data on manipulating the statistical analysis data for the purpose of concealing the low accuracy of the model [7].

With this background, our research was carried out in the prospective design, allowing for determining the accuracy and quality of AI operation in the settings of practical healthcare. For the first time ever, quite a vast set of material was used to obtain the parameters of accuracy and stability of AI-service operation for the morphometry of the prostate gland, distinct by its scientific novelty. The obtained clinical measurement value of 92.0% indicates the sufficiently high accuracy of the tested AI-service operating with the real flow of radiodiagnostics data. At the same time, the analysis of the structure of the defects has allowed for objectively detecting problems with the segmentation of the target organ. Based on the experience of the Moscow Experiment, incorrect segmentation is a typical error of the AI-services, especially often occurring at the early stages of their development (for this specific clinical task) [7]. The studied AI-service was introduced into the experiment relatively recently, which is why the said type of defect is quite explainable. The results of the clinical monitoring can be used both for the elimination of specific defect and for the general improvement of the AI-service along with its preparation for clinical testing for the purpose of receiving the status of the medical device.

Research limitations

The research work included only one software product based on AI technologies. This situation is due to the absence of other developments capable of solving the tasks of automated morphometry of the prostate gland. As of the date of 01.03.2025, in the Russian Federation, there are no AI-based devices for solving this challenge; the research includes only one relevant participant of the Moscow experiment. Evidently, certain measures are required for stimulating the development of other solutions, including the ones having the functional capabilities of supporting the diagnostic decisions based on the radiomics.

CONCLUSION

The automatization of routine measurements greatly contributes to standardizing the processes of describing the results of radio-diagnostic examinations. This aspect has a special importance from the point of view of providing the continuity of medical aid in cases of the patient presenting to various medical organizations.

The AI technologies are applicable for the automatization of the prostate gland measurements when describing the results of MRI-scanning of the lesser pelvis organs. The experience of using the corresponding AI-service in the settings of practical healthcare has shown the clinical measurement value of 92.0%, which allows for characterizing the accuracy and the quality of its operation in a flow of MRI-scanning results as high.

The obtained data can be used as the methodical material for developing other products for the automated morphometry of the prostate gland based on the results of MRI-scanning of the lesser pelvis.

ADDITIONAL INFORMATION

Author contributions. *N.M. Nasibian:* literature review, data collection and processing, analysis of results, manuscript preparation; *A.V. Vladzymyrskyy:* study conception, final editing, manuscript approval; *K.M. Arzamasov:* final editing, manuscript approval. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval. This study was carried out in accordance with the framework established by the Experiment on the Use of Innovative Technologies in Computer Vision for Medical Image Analysis, with subsequent applications in the healthcare system of Moscow. The research received approval from the ethical committee, as documented in protocol No. 2 of IEC of MRB of the RSR dated February 20, 2020. Additionally, the study is registered on ClinicalTrials under the identifier NCT04489992. All patients whose images were included in the study signed an informed voluntary consent upon admission to the hospital to use the results of the examination and treatment for scientific purposes.

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Optimizing the Fluorescent Visualization with Indocyanine Green During Laparoscopic Cholecystectomy

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ABSTRACT

BACKGROUND: *The prevention of damaging the bile ducts during surgical interventions in patients with calculous cholecystitis remains a topical problem in modern abdominal surgery. The incidence of damaging the bile ducts reaches 0.4–2%, while in cases of complicated forms — up to 5.2%.* ***AIM:*** *determining the optimal dosage and timing of administering the Indocyanine green (ICG) for increasing the efficiency of fluorescent cholangiography during the course of laparoscopic cholecystectomy in cases of calculous cholecystitis. The top-priority task of the research is minimizing the risks of injuring the bile ducts by means of clear intraoperative visualization of the extrahepatic bile ducts.* ***METHODS:*** *Prospective non-randomized research was conducted within the premises of the University Clinical Center named after V.V. Vinogradov (affiliated branch) of the RUDN University during the period from March 2024 until April 2025. The research included 276 patients undergoing the laparoscopic cholecystectomy with using the ICG-cholangiography. The dosages of Indocyanine green used (1.25 mg; 2.5 mg; 5 mg; 10 mg) were administered in various time periods before starting the surgery (from 40 minutes up to 6 hours), as well as intraoperatively. The evaluation included the degree of fluorescence, the time from the moment of administering the Indocyanine green until the optimal fluorescence of the bile ducts and of the liver required for the safe conduction of laparoscopic cholecystectomy, as well as the possibility to correct the hyper- and hypofluorescence by changing the equipment settings.* ***RESULTS:*** *Optimal visualization of the extrahepatic bile ducts was observed at a dosage of 5 mg of ICG 3–5 hours after the administration, for the 2.5 mg dosage — 2–3 hours, while for the 1.25 mg dosage, the time was 40–120 minutes. Intraoperative administration of 1.25 mg provided a rapid visualization, but caused hyperfluorescence, complicating the determination of the topography of bile ducts, which was corrected by equipment settings.* ***CONCLUSION:*** *Fluorescent cholangiography with using the Indocyanine green is a safe and effective method of visualizing the extrahepatic bile ducts during laparoscopic cholecystectomy. The most optimal dosages of Indocyanine green are the following: 1.25 mg — 40–120 minutes, 2.5 mg — 2–3 hours and 5 mg — 3–5 hours before the intervention. The 1.25 mg dosage can be administered intraoperatively with further correction of equipment settings at the menu of the video-system (by lowering the enhancement and the intensity parameters) for decreasing the hyperfluorescence effect.*

Keywords: *calculous cholecystitis; indocyanine green; fluorescence visualization; laparoscopic cholecystectomy; dose optimization.*

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BACKGROUND

The prevention of damaging the bile ducts during surgical interventions in patients with calculous cholecystitis remains a topical problem in modern abdominal surgery. [1, 2]. According to worldwide statistics, each year more than a million of laparoscopic cholecystectomies are carried out for calculous cholecystitis [3, 4], with the rates of damaging the bile ducts reaching 0.4–2% and up to 5.2% for complicated forms, according to the data from foreign registries [5, 6]. The main reason of damaging the bile ducts is the inadequate intraoperative identification of the anatomic structures, especially in the settings of inflammatory changes and infiltration of tissues [7].

The method of fluorescent laparoscopy and fluorescent cholangiography with using the Indocyanine green (ICG), implemented at the real time mode, opens new possibilities in increasing the safety

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Оптимизация флюоресцентной визуализации с индоцианином зелёным при лапароскопической холецистэктомии

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АННОТАЦИЯ

Обоснование. *Профилактика повреждений желчевыводящих путей при оперативных вмешательствах у больных с калькулёзным холециститом остаётся актуальной проблемой в современной абдоминальной хирургии. Частота повреждений желчных протоков достигает 0,4–2%, а при осложнённых формах — до 5,2%.* ***Цель исследования*** *— определить оптимальную дозировку и время введения индоцианина зелёного (ICG) для повышения эффективности флюоресцентной холангиографии во время лапароскопической холецистэктомии при калькулёзном холецистите. Приоритетной задачей исследования является минимизация риска травм желчных путей посредством чёткой интраоперационной визуализации внепечёночных желчных протоков.* ***Методы.*** *Проспективное нерандомизированное исследование проведено на базе Университетского клинического центра имени В.В. Виноградова (филиал) РУДН в период с марта 2024 по апрель 2025 года. В исследование включены 276 пациентов, которым выполнена лапароскопическая холецистэктомия с применением ICG-холангиографии. Использованы дозы индоцианина зелёного (1,25 мг; 2,5 мг; 5 мг; 10 мг), вводимые в разные временные промежутки до начала операции (от 40 минут до 6 часов), а также интраоперационно. Оценивались интенсивность флюоресценции, время от момента введения индоцианина зелёного до оптимального свечения желчных протоков и печени для безопасного выполнения лапароскопической холецистэктомии, а также возможность нивелировать гипер- и гипофлюоресценцию изменением настроек оборудования.* ***Результаты.*** *Оптимальная визуализация внепечёночных желчных протоков отмечена при дозе 5 мг ICG через 3–5 часов после введения, при дозе 2,5 мг — через 2–3 часа, при дозе 1,25 мг — через 40–120 минут. Интраоперационное введение 1,25 мг обеспечивало быструю визуализацию, но вызывало гиперфлюоресценцию, затрудняющую определение топографии желчных путей, которая нивелировалась настройками оборудования.* ***Заключение.*** *Флюоресцентная холангиография с использованием индоцианина зелёного является безопасным и эффективным методом визуализации внепечёночных желчных протоков при лапароскопической холецистэктомии. Наиболее оптимальные дозировки индоцианина зелёного: 1,25 мг за 40–120 минут, 2,5 мг за 2–3 часа и 5 мг за 3–5 часов до вмешательства. Доза 1,25 мг может быть введена интраоперационно с последующей коррекцией настроек оборудования в меню видеосистемы (снизить показатели усиления и насыщенности) для уменьшения эффекта гиперфлюоресценции.*

Ключевые слова: *калькулёзный холецистит; индоцианин зелёный; флюоресцентная визуализация; лапароскопическая холецистэктомия; оптимизация дозы.*

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of laparoscopic interventions. Especially important is the high accuracy of visualization in case of significant inflammation, which limits the possibilities of standard anatomical orientation.

Research aim — determining the optimal dosage and timing of administering the Indocyanine green (ICG) for increasing the efficiency of fluorescent cholangiography during the course of laparoscopic cholecystectomy in cases of calculous cholecystitis. The top-priority task of the research is minimizing the risks of injuring the bile ducts by means of clear intraoperative visualization of the extrahepatic bile ducts.

METHODS

Research design

Prospective non-randomized.

Conformity criteria

Inclusion criteria: patients aged over 18 years; confirmed (by the data from instrumental examinations) diagnosis of calculous cholecystitis; signed informed consent.

Non-inclusion criteria: patients aged under 18 years; pregnancy

Exclusion criteria: patient not presenting for hospitalization, refusal to undergo treatment.

Research facilities

The examination was carried out within the premises of the Department of Intermediate Level Surgery under the Medical Institute of the Federal State Autonomous Educational Institution of Higher Education "Patrice Lumumba Peoples' Friendship University of Russia" at the University Clinical Hospital named after V.V. Vinogradov.

Research duration

The research activities lasted from March 2024 until April 2025.

Medical procedure description

On admission, all the patients were examined in accordance with the current clinical recommendations from the Ministry of Health of the Russian Federation. The diagnosis of calculous cholecystitis was the indication for conducting the laparoscopic cholecystectomy with intraoperative fluorescent cholangiography.

For the fluorescent cholangiography, an intravenous administration of domestically manufactured Indocyanine green («Life Sciences — Obninsk Chemical-Pharmaceutical Company" LLC) was conducted at dosages ranging from 1.25 to 10 mg. The standard packaging of the product is 25 mg of lyophilized product per vial, intended for dissolving in 10 ml of water for injections before use.

The recommended dosages mentioned in the package leaflet vary from 0.25 to 0.5 mg/kg, however, the literature data contain lower values — 0.1–0.2 mg/kg [8]. The practical experience shows that the fluorescence effect depends to a greater extent on the quantity of the product and on the timing of its administration rather than on the body weight-based calculations, which is related to the technical characteristics and the sensitivity of the equipment along with the sufficient level of the drug product accumulation in the hepatobiliary system.

Methods for registration of outcomes

During the course of the research, the employed equipment was from the leading manufacturers, having various characteristics of infrared radiation with a wavelength for the excitation of fluorescence ranging from 780 nm to 805 nm: Arthrex 4K (USA), ELEPS 4K (Russia), Rubina Carl Storz 4K (Germany), Olympus OTV-S200 (Japan), Stryker PINPOINT HD (Canada), Olympus OTV-S700 (Japan).

The evaluation of the efficiency of fluorescence was conducted visually using the monitor screen. The sufficient level was considered the one at which there was a clearly detectable topography of structures of the hepatoduodenal ligament and of the Calot's triangle.

The obligatory criterion for surgical safety was achieving the critical view of safety (CVS). The surgeries were carried out using the uninterrupted fluorescence mode at all the stages.

Statistical analysis

For representing the results and for the statistical processing of the data, the Microsoft Excel software was used. Data were presented as the mean values ± standard deviation.

RESULTS

Research sample (participants)

The research included 276 patients with clinically and instrumentally confirmed diagnosis of calculous cholecystitis, of which there were 78 (28.3%) men and 198 (71.7%) women, the mean age was 65.0±15.6 years and the mean body mass index was 32.2±5.78 kg/m^2.

Laparoscopic cholecystectomy with using the ICG-cholangiography was carried out for all the 276 patients with various dosages.

During the initial stage of the research, in 5 (1.8%) patients, the dosage used was 10 mg with the administration 6–8 hours before surgery, which was accompanied by significant intraoperative fluorescence of the liver, of the gall bladder and of the extrahepatic bile ducts, complicating the differentiation of anatomic structures and hindering the confident dissection at the Calot's triangle. Later on, during the time periods ranging from 1 to 5 hours from the moment of administering the drug product and before the initiation of surgery, the dosages of 5 mg (in 72 patients, 26.1%), 2.5 mg (in 116, 42.0%) and 1.25 mg (in 83, 30.1%) were tested.

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Main research outcomes

In a group of patients with a 5 mg dosage (*n*=72), the best conditions for the visualization were achieved in the interval of 3–4 hours from the moment of administering the ICG. In this time interval, clear fluorescence was observed for the extrahepatic bile ducts with minimal background fluorescence or its absence in the hepatic parenchyma. In the time interval from 1 to 3 hours, hyperfluorescence was reported, which was hindering the isolation of the cystic duct, the identification and the determination of the topography of the common bile duct. In the time interval of 3–4 hours from the moment of administering the ICG, hepatic fluorescence was not observed and clear differentiation was achieved for the cystic duct and for the common bile duct at the real time mode. As for the time interval of 4–5 hours, the visualization persisted, however, the intensity of fluorescence was slightly decreased, requiring the light source to be moved closer.

In the second group (*n*=116), the Indocyanine green dosage used was 2.5 mg. The drug was administered 1–4 hours and more before the initiation of the intervention.

In this group, at an interval of 2–3 hours, the best visualization was achieved: hypofluorescence of the hepatic parenchyma with optimal fluorescence of the extrahepatic bile ducts. When administering the ICG 1–2 hours before surgery, hyperfluorescence was observed, as a result of which, the tissues had an intensive generalized fluorescence, which hindered the differentiation of the structures in the Calot's triangle. After 3 hours, the intensity of fluorescence was decreasing, but the anatomical characteristics remained distinguishable. After the expiration of 4 hours, there was only a weak fluorescent effect observed, which required adjusting the equipment settings.

In a group of 83 patients, the drug was administered at a dosage of 1.25 mg intraoperatively 90 minutes before the surgical intervention.

Upon administering the Indocyanine green intraoperatively (40 minutes before surgery) the observed findings in the patients included significant fluorescence of the liver and of the gall bladder, as well as of the hepatoduodenal ligament area, which, at the beginning of surgery, hindered the accurate anatomical identification of extrahepatic bile ducts. With the time interval of administering the ICG ranging from 40 to 120 minutes, the intensity of fluorescence was decreasing to the comfortable level, which allowed for determining the topography of extrahepatic bile ducts and to safely conduct surgery with the fluorescence mode turned on. The summarized data on the dosages and the time intervals of administering the ICG are provided in table 1, with the data on the optimal fluorescence periods — in table 2.

The technical capabilities of the equipment allow for adjusting the visual intensity of fluorescence (hyper- and hypofluorescence): for this, in the settings menu of the video-system assembly, in the fluorescence mode section, it is necessary to adjust the enhancement and the intensity depending on the requirements. The brightness and the contrast ratio can be adjusted for the visual comfort of the surgeon.

Undesirable phenomena

Based on the results of the research, in a group of 276 patients undergoing the laparoscopic cholecystectomy with ICG-fluorescent visualization of the extrahepatic bile ducts, no complications were observed. In 23 (8.3%) patients, the complications were successfully avoided by clear following the technique of critical view safety (CVS) and by using the intraoperative fluorescent ICG-cholangiography (examples provided in Fig. 1, 2).

Table 1

Dosages and time intervals of administering the Indocyanine green (ICG)

Dosage, mg	Time interval, h	Number of patients, *n* (%)
5	1–3	15 (20.8)
	3–4	34 (47.3)
	4–5	23 (31,9)
2.5	1–2	19 (16.3)
	2–3	69 (59.5)
	3–4	25 (21.7)
	>4	3 (2.5)
1.25	≤40 min.	32 (38.5)
	40–120 min.	51 (61.5)

Table 2

Optimal fluorescence windows

Dosage, mg	Intraoperative administration	1–2 hours	2–3 hours	3–4 hours	4–5 hours
5					
2.5					
1.25					

Designation	
	Hyperfluorescence — difficult to differentiate the structures
	The intensity of hepatic staining is decreased
	Optimal fluorescence window
	Hypofluorescence — weak fluorescence

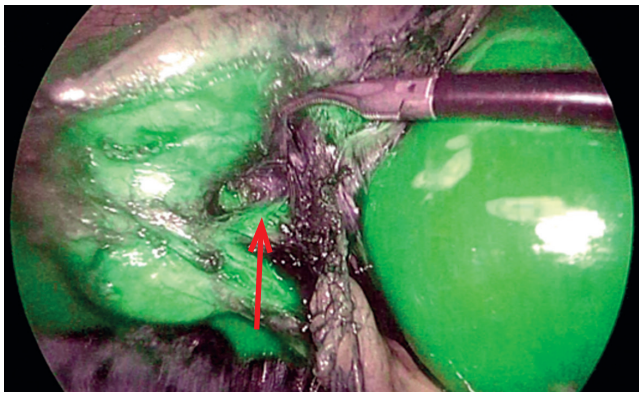

Fig. 1. Mirizzi syndrome: tight fusion of the Hartmann pouch with the hepatic duct (arrow) due to inflammation (incipience of Mirizzi syndrome formation).

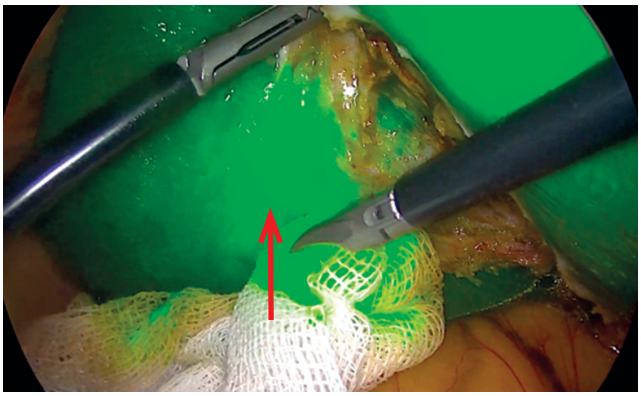

Fig. 2. Damage of the subsegmental duct: bile leakage after damage to the subsegmental duct (arrow).

DISCUSSION

The dissection of the area of the Calot's triangle during the laparoscopic cholecystectomy is an important surgical step, during which, serious iatrogenic complications can develop [8]. The accurate identification of the cystic duct and of the cystic artery can be quite difficult in cases of significant inflammatory changes or rare anatomic variations in this zone. In such situations, fluorescent visualization provides potentially great benefits, facilitates the course of the surgery and allows for avoiding the damage of the common bile duct [9]. However, as of today, there is no commonly accepted standard of conducting the fluorescent laparoscopy during cholecystectomy [10]. ICG is a widely used water-soluble staining agent, which is completely metabolized by the liver and excreted solely via the bile ducts [11]. The main mechanism of action is based on the fluorescence produced by the ICG staining agent upon the exposure of light in the near infrared range, which allows for visualizing the anatomical structures by means of a specialized visualization system [12]. The method allows for selectively highlighting various structures, including blood vessels, bile ducts and lymphatic vessels, however, the variation of dosage and time of administered ICG significantly affects the quality of fluorescent visualization [13]. In particular, lower dosages of ICG can increase the total visualization time, while higher dosages increase the intensity of the fluorescent signal [13].

Despite the great theoretical benefits of fluorescent laparoscopy with ICG during surgical interventions in the biliary excretion system, currently its clinical application is mainly experimental. In the systematic review by M. Manasseh et al. [10], the results of 14 research works were analyzed, which have demonstrated the safety of the method and its benefits in the complex cases, with this, only in single research works, the optimal dosage of the staining agent and the timing of its administration were determined. There are currently ongoing active discussions regarding the optimal ICG dosage [14].

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A foreign research arranged by the group headed by F. Pardo Aranda [13] has demonstrated the results similar to ours — the best visualization being achieved upon administering 2.5 mg of ICG to the patients 2–6 hours before surgery. Notably, this dosage was not adjusted depending on the weight of the patient or the body mass index, otherwise this variability could hinder the precise preparation of ICG solutions and could significantly increase the labour-intensity for the medical staff.

Thus, for achieving the optimal fluorescence window, the following dosages are recommended: 5 mg — when injecting 3–5 hours before surgery; 2.5 mg — when injecting 2–3 hours before surgery; 1.25 mg — when administering 40–120 minutes before surgery. Intraoperative administration of 1.25 mg ICG can be used, if necessary, but it requires changing the settings in the video-system.

CONCLUSION

In our research, we tried to investigate the effects of various dosages of domestically manufactured ICG on the intraoperative visualization and their effects on the surgical and post-operative results. This is the first ever research involving the usage of the domestically manufactured staining agent.

Intraoperative fluorescent cholangiography with using the Indocyanine green proves its safety and efficiency in the prevention of damaging the extrahepatic bile ducts during the course of laparoscopic cholecystectomy in patients with calculous cholecystitis, while the possibility of adjusting the fluorescence intensity by changing the equipment settings together with selecting the optimal dosages makes the fluorescent visualization technology controllable.

ADDITIONAL INFORMATION

Author contributions. *M.V. Kosachenko*: processing and discussion of research results, manuscript writing; *A.M. Leonovich, A.V. Burlakova*: search and analytical operations, discussion of research results, manuscript writing; *A.E. Klimov*: managing the treatment of patients and discussing the research results. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Evaluation of Efficiency of the Impact of Vitamin D and Remineralizing Toothpaste on the Structure of the Dental Enamel in the Individuals with Homozygous Polymorphism in the Gene, Encoding the Intracellular Vitamin D Receptor (VDR)

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ABSTRACT

BACKGROUND: *Only a few literature sources data show the relation of the VDR gene polymorphism and the susceptibility to developing dental caries. Within this context, investigating the structure of the dental enamel and the changes of its resistance under the effects of vitamin D and remineralizing therapy among the persons with the homozygous polymorphism of the VDR gene (A/A) is topical.* ***AIM:*** *to investigate the effects of vitamin D and the toothpaste with remineralizing contents on the structure of the enamel surface of the impacted teeth extracted from the individuals with homozygous polymorphism of the VDR gene.* ***METHODS:*** *In 2023–2025, within the premises of the Dentistry Department of the Federal State Budgetary Institution of Continuing Professional Education "Central State Medical Academy", a total of 200 students aged 22–25 years were screened with undergoing a genetic testing to reveal the polymorphism of the VDR gene. Out of the 36 assessed subjects, 18 individuals were detected with the homozygous A/A allele that are currently undergoing orthodontic therapy and requiring an extraction of the impacted molars. A total 24 of extracted teeth were tested with submerging them into the artificial saliva with an addition of various media. The dental samples were distributed into four groups: only artificial saliva (I, control); 1000 IU of cholecalciferol per 100 ml (II); processing with remineralizing toothpaste (III); vitamin D and remineralizing toothpaste (IV). The evaluation of the structure of the dental enamel was carried out using the method of confocal profilometry with measuring the Ra and Rp roughness parameters.* ***RESULTS:*** *In group II with the presence of cholecalciferol, changes were revealed in the roughness parameters (Ra, Rp) of dental enamel surface, in group III (processing with remineralizing toothpaste) the Ra and Rp parameters had similar digital values. As for the samples from the group IV, comparing to the group I, smoothness was revealed in the dental enamel surface, which is confirmed by the Ra and Rp ($p > 0.001$) parameters. This effect can be explained by the synergic action of the cholecalciferol and the remineralizing components of the toothpaste on the structure of the enamel.* ***CONCLUSION:*** *In the individuals with homozygous polymorphism (A/A) of the VDR gene, significant changes were revealed in the parameters of dental enamel roughness (Ra and Rp) after the combined use of cholecalciferol and remineralizing toothpaste, which is related to the smoothening of surface due to the formation of the homogeneous layer consisting of the microRepair microcrystals.*

Keywords: *polymorphism; VDR gene; confocal profilometry; remineralizing toothpaste; vitamin D; cholecalciferol.*

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BACKGROUND

According to the results of researches on dental health, the incidence and the intensity of dental caries remains high despite the conducted prevention measures and modern treatment methods [1].

The susceptibility of dental enamel to the effects of cariogenic factors is mainly determined by its

Оценка эффективности действия витамина D и реминерализирующей пасты на структуру эмали зубов у лиц с гомозиготным полиморфизмом гена, кодирующего внутриклеточный рецептор витамина D

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АННОТАЦИЯ

Обоснование. *Единичные литературные данные указывают на связь полиморфизма гена внутриклеточного рецептора витамина D (VDR) с предрасположенностью к развитию кариеса. В связи с этим изучение структуры эмали зубов и изменений её резистентности под действием витамина D и реминерализирующей терапии у лиц с гомозиготным полиморфизмом гена VDR (A/A) является актуальным.* ***Цель исследования*** *— изучить действие витамина D и зубной пасты с реминерализирующим составом на структуру поверхности эмали удалённых ретенированных зубов у лиц с гомозиготным полиморфизмом гена VDR.* ***Методы.*** *В 2023–2025 годах на кафедре стоматологии ФГБУ ДПО ЦГМА обследовано 200 обучающихся в возрасте 22–25 лет, которым проведён генетический тест на определение полиморфизма гена VDR. Выявлено 18 человек с гомозиготным аллелем A/A, находившихся на ортодонтическом лечении и нуждающихся в экстракции ретенированных моляров. Изучали 24 удалённых зуба, которые помещали в искусственную слюну с добавлением различных сред. Образцы зубов распределены на четыре группы: только искусственная слюна (I, контроль); холекальциферол 1000 МЕ на 100 мл (II); обработка реминерализирующей пастой (III); витамин D и реминерализирующая паста (IV). Исследование структуры эмали зубов проводили методом конфокальной профилометрии с измерением показателей шероховатости Ra и Rp.* ***Результаты.*** *В группе II в присутствии холекальциферола выявлены изменения показателей (Ra, Rp) шероховатости поверхности эмали зубов, в группе III (обработка реминерализирующей пастой) показатели Ra и Rp имели аналогичные цифровые значения. У образцов зубов группы IV в сравнении с группой I отмечена сглаженность шероховатости поверхности эмали, что подтверждают параметры Ra и Rp (p >0,001). Данный эффект можно объяснить синергическим действием холекальциферола и реминерализирующего состава зубной пасты на структуру эмали.* ***Заключение.*** *У лиц с гомозиготным полиморфизмом (A/A) гена VDR установлено достоверно значимое изменение параметров шероховатости эмали зуба (Ra и Rp) при комплексном использовании холекальциферола и реминерализирующей зубной пасты, что связано с выравниванием поверхности за счёт образования гомогенного слоя, состоящего из микрокристаллов.*

Ключевые слова: *полиморфизм; ген VDR; конфокальная профилометрия; реминерализирующая паста; витамин D; холекальциферол.*

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structural features, which also depend on various genetic variations [2].

There are quite few research works proving that the polymorphism of the gene encoding the intracellular vitamin D receptor (VDR Bsml rs1544410) is the reason of vitamin D deficit [3, 4]. X. Qin et al. [5] have reported the interrelation between low blood cholecalciferol levels and high incidence of dental caries.

Previously, in the individuals with homozygous polymorphism (A/A) of the VDR gene, the experiment on evaluating the enamel structure using the electron scanning microscopy has shown the morphological

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changes in its surface, resulting from the demineralization process. The results of spectrometric analysis have confirmed the activation of the hard tooth tissues resorption phase, which manifested as an impairment of the microelement content [6]. According to the modern concept from the World Health Organization, one of the most effective strategies for caries prevention is the remineralizing therapy [7–9]. The preventive and therapeutic effects of mineral elements (phosphorus, calcium, fluorine) are based on their inclusion into the crystalline lattice formed by the dental enamel apatites [10].

There are data on the effective endogenous prevention of caries expressed as an additional intake of vitamin D, affecting the calcium-phosphorus metabolism [11].

In patients with homozygous A/A genotype, blood vitamin D deficit takes place, being the reason of impaired calcium metabolism and of developing a dysbalance of bone tissue remodeling [12].

One of the variants of experimental evaluation of the dental enamel structure is the confocal optical profilometry [13], allowing for the assessment of the enamel surface with using the digital methods and for conducting the statistical analysis of the results.

Research aim — to evaluate the effects of using vitamin D and toothpaste with remineralizing components on the structure of dental enamel of the impacted teeth extracted from the individuals with homozygous (A/A) VDR gene polymorphism.

METHODS

Research design

The conducted research is classified as experimental single-center prospective full-design controlled and randomized research (Fig. 1).

SCREENED
200 individuals aged 22–25 years (68 males, 132 females),
studying at the Dentistry Department of the FSBI CPE CSMA in 2023–2025

GENETIC TESTING
Assessment of the *VDR* genotypes (BsmI rs1544410)

Inclusion criteria	Non-inclusion criteria
• patients with detected homozygous (A/A) polymorphism of the *VDR* gene and diagnosed with vitamin D deficit treated with daily intake of cholecalciferol at a dosage of 1000 IU, having the orthodontic indications to extracting the third molars of the mandible, with the diagnosis of "K07.35 Impacted or unerupted teeth" • extracted third mandibular molars with a developed anatomical structure in the abovementioned patients	• screened individuals with the diseases of the gastrointestinal tract, kidneys abnormalities, oncological, autoimmune or endocrine diseases • pregnancy, breastfeeding

36 assessed (16 males, 20 females) with homozygous polymorphism (A/A)
of the *VDR* gene (BsmI rs1544410) and blood vitamin D deficit

24 extracted (according to the orthodontic indications) impacted lower molars
placed into the containers with artificial saliva (4 groups of 6 teeth)

I, control	II	III	IV
only artificial saliva	+ cholecalciferol 1000 IU per 100 ml of solution	+ treatment with remineralizing toothpaste	+ cholecalciferol 1000 IU per 100 ml of solution + treatment with remineralizing toothpaste

CONFOCAL OPTICAL PROFILOMETRY

Fig. 1. Research design.

Within the premises of the Dentistry Department of the Federal State Budgetary Institution of Continuing Professional Education "Central State Medical Academy" (FSBI CPE CSMA), 200 students aged 22–25 years were examined (68 males and 132 females) with conducting the tests for determining the VDR gene polymorphism (BsmI rs1544410).

Conformity criteria

Inclusion criteria: patients with detected homozygous (A/A) polymorphism of the VDR gene and with diagnosed vitamin D deficit despite the daily intake of cholecalciferol at a dosage of 1000 IU, having the orthodontic indications to extracting the third mandibular molars, with the diagnosis of "K07.35 Impacted or unerupted teeth"; the extracted third mandibular molars had a developed anatomical structure in all of the abovementioned patients.

Non-inclusion criteria: individuals with gastrointestinal tract diseases, abnormalities in the kidneys, oncological, autoimmune or endocrine diseases; pregnancy, breastfeeding.

Research facilities

The clinical research itself, the procedures of collecting the genetic material and the extraction of the impacted mandibular molars were arranged within the premises of the Dentistry Department of the FSBI CPE CSMA.

The genetic testing purposed to reveal the polymorphism of the VDR gene encoding the intracellular vitamin D receptor was carried out at the "MyGenetics" National Center of Genetic Tests (Novosibirsk).

The measurements of the dental enamel roughness parameters were conducted using the S Neox confocal optical profilometer (Sensofar, Spain) at the Federal State Budgetary Scientific Institution "Technological Institute for Superhard and Novel Carbon Materials" under the National Research Center "Kurchatov's Institute" (Moscow, Troitsk).

Research duration

The research was carried out during the period from 2023 until 2025.

Medical procedure description

In patients with homozygous polymorphism (A/A) of the VDR gene (*n*=18), using the conduction and infiltration anesthesia with Ultracaine D-S forte (Sol. Ultracaini forte) at the volume of 1.7 ml, the formation and the delamination of the mucoperiosteal flap was carried out at the level of the third mandibular molar projection, then, using the fissural dental drill, the bony operculum was removed, followed by the extraction of the impacted teeth using the elevator tool. Later on, the mucoperiosteal flap was positioned back to its place and sutured using simple interrupted sutures. A total of 24 teeth were extracted.

Research outcomes

Main research outcome: the extracted teeth were cleared of the soft tissues and placed into the flasks containing the artificial saliva (structurized water; electrolytes: Na^+ 0.3 g/l, K^+ 1 g/l, Ca^{2+} 0.05 g/l, Mg^{2+} 0.01 g/l, Cl^- 0.1 g/l, $(PO)_4^{3-}$ 0.1 g/l; organic substances: 0.5% carboxymethylcellulose and alginic acid, urea). The dental samples in quantities of six were placed into four flasks according to the following groups: group I contained only the artificial saliva solution (hereinafter referred to as the Control group); in group II, the solution of artificial saliva was supplemented with cholecalciferol at a concentration of 1000 IU/100 ml; in group III, into the enamel of the extracted teeth, by means of the electric tooth brush, toothpaste was rubbed in for 2 minutes twice daily (following the 10 hours interval), with the paste containing the microRepair microcrystals; in group IV, the extracted teeth processed with the toothpaste according to group III protocol, were placed into the flask containing the artificial saliva with cholecalciferol at a concentration of 1000 IU/100 ml.

The flasks were stored at the incubation chamber at 37°C for 72 hours, after which the teeth were taken out and washed with water for 60 seconds.

Methods for registration of outcomes

The measurements in the dental enamel roughness parameters were made at the contact surface of the molars at the level of the tooth equator using the diagonal and the horizontal profiles by means of the S Neox confocal optical profilometer (Sensofar, Spain). The three-dimensional images of the surface were obtained with the ×50 objective lens (vision field dimensions 351×264 μm, resolution 0.13 μm) with using the LED (Light Emitting Diode) light source at various wavelengths: red (630 nm), green (530 nm), blue (460 nm) and white.

The digital processing of the dental enamel surface scans was conducted using the Senso SCAN and Gwyddion software products.

The procedures of evaluating the roughness parameters of the enamel surface were carried out in

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accordance with the State Industry Standard (GOST) R ISO 25178-2-2014[1], regulated by the State Industry Standard (GOST) 2789-73. The automatic data calculations were done using the Sensofar software (in accordance with ISO 4287).

The following parameters were evaluated within the ranges of the basic length, allowing for interpreting the changes in the dental enamel surface roughness at the stages of the experiment: Ra (average roughness) — the arithmetic mean of the deviations in the estimated profile; Rp (maximum peak height) — the maximal peak height within the profile.

Statistical analysis

For the statistical processing of the results and for describing the data, the Statistica 13.3 (StatSoft Inc.) and the GraphPad Prism 9 version 9.4.1 software products were used. The mean values of the parameters were provided as M±m, where M is the mean value and m is the error of the mean. The statistically significant differences taken into account were the ones with the significance level (*p*) not exceeding 0.05.

RESULTS

Research sample (participants)

Within the premises of the Dentistry Department of the FSBI CPE CSMA, a total of 200 students aged 22–25 years (68 males and 132 females) were screened and underwent testing purposed to determine the polymorphism of the VDR gene (Bsml rs1544410).

Based on the results of genetic testing, the group with homozygous A/A allele of the VDR gene consisted of 36 individuals (16 males and 20 females) with diagnosed vitamin D deficit (blood serum concentration was 9.04±2.02 ng/ml). From this group, 18 individuals were selected (7 males, 11 females), in which, due to the presence of orthodontic indications, an extraction of the third mandibular molars was carried out (diagnosis: “K07.35 Impacted or unerupted teeth”).

Primary findings

In the individuals with homozygous polymorphism (A/A) of VDR gene, the microstructure of the dental enamel samples stored in the artificial saliva solution (group I, control) had changes in the structural profile. The three-dimensional image of the surface of dental sample, provided in Fig. 2, had a characteristic pattern of numerous peak-like elevations above the baseline surface, presented as an inhomogeneous plane of predominantly red color. Fig. 3 shows the graphic profile of such surface, having a high rate of alternating peaks and valleys. After the digital processing of the obtained data, the Ra value was determined, which equals 0.436±0.052 upon measuring in the diagonal direction and 0.308±0.172 for the horizontal direction (Fig. 4), along with the values of the maximal height variation of the Rp — 1.421±0.16 and 1.440±0.46, respectively (Fig. 5).

[1] National Standard of the Russian Federation. GOST R ISO 25178-2-2014. The geometric characteristics of the products (GPS). Access mode: https://docs.cntd.ru/document/1200116349?ysclid=mc1xy4b8js53577141

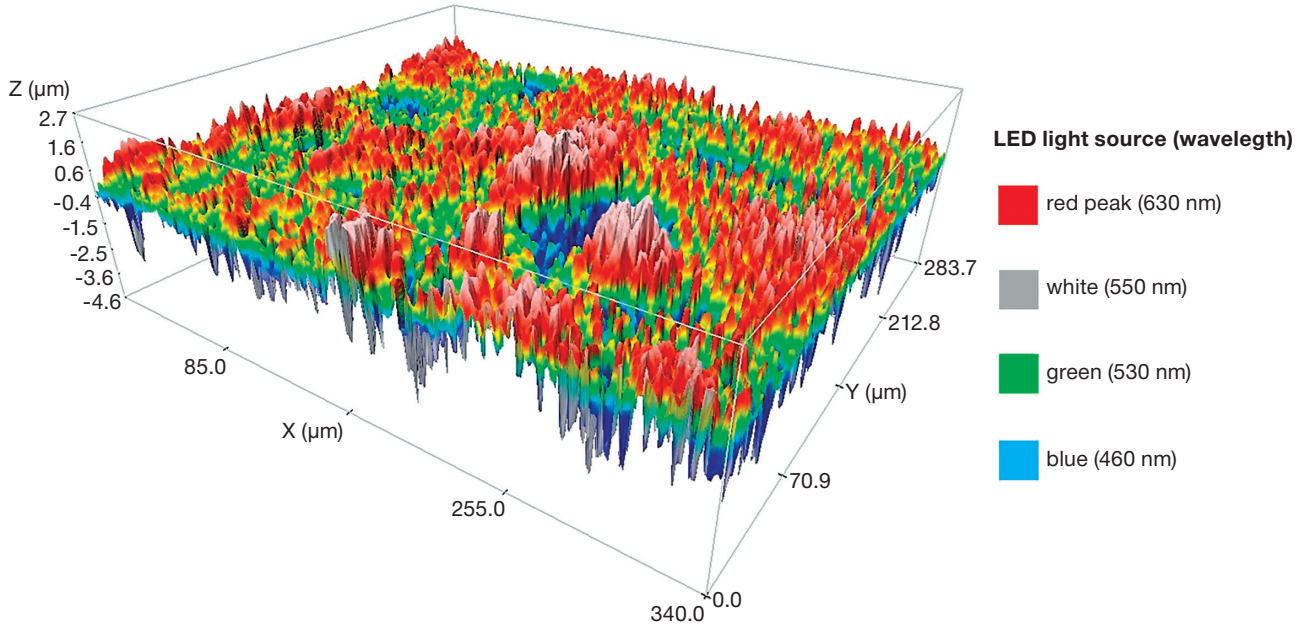

Fig. 2. Three-dimensional image of the enamel surface sample from group I.

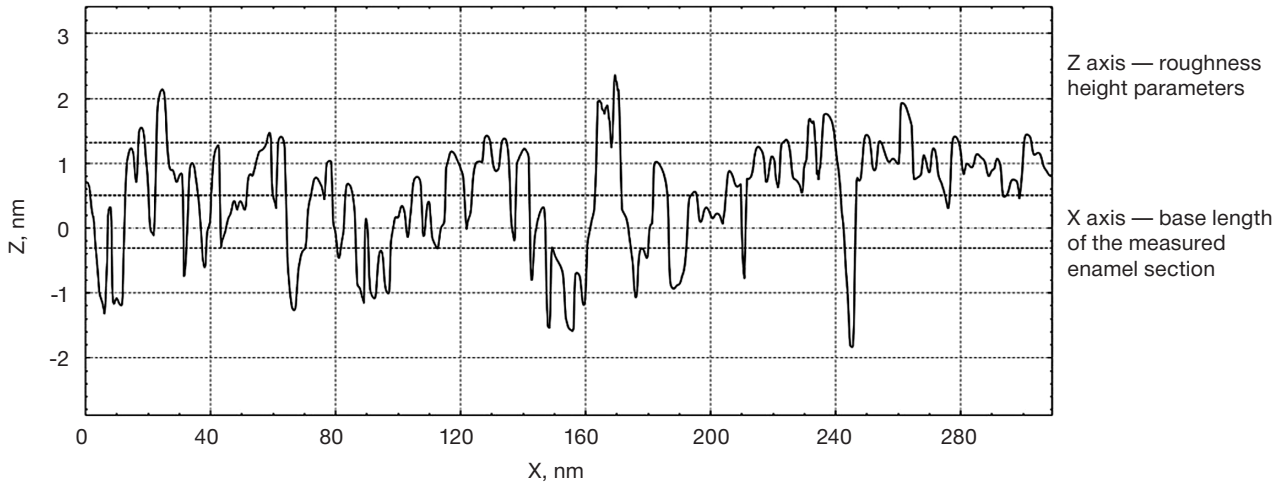

Fig. 3. Enamel surface profile of the sample from group I.

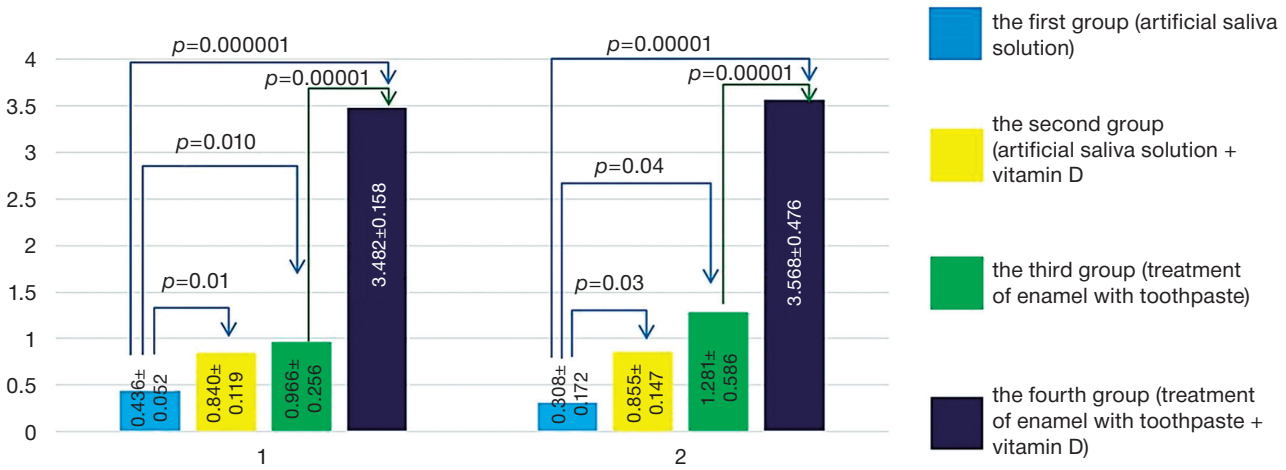

Fig. 4. Ra parameter chart (the arithmetic mean of the deviations for the estimated profile: 1 — diagonal measurement; 2 — horizontal measurement).

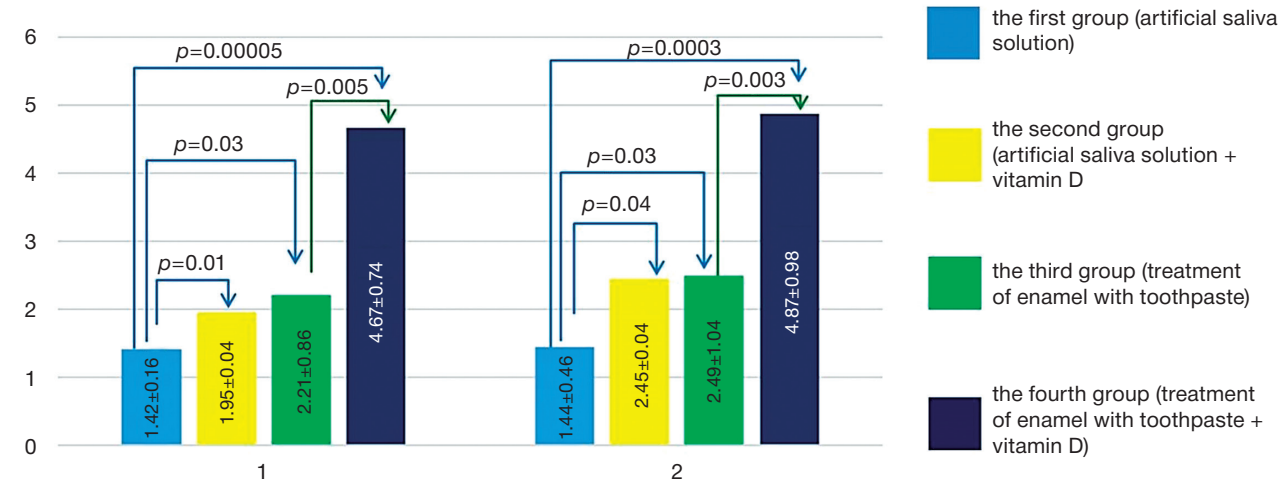

Fig. 5. Rp parameter chart (maximum height of the profile peak: 1 — diagonal measurement; 2 — horizontal measurement).

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The enamel surface in the extracted impacted teeth from the group II with an addition of 1000 IU of cholecalciferol to the artificial saliva solution, upon the analysis of its three-dimensional images, had an enlarged area of the green and blue-colored fields (Fig. 6). The graphic representation of the height peaks has shown a moderate variation between the highest and the lowest points of the roughness line graph (Fig. 7). After the digital evaluation of the surface profile, the Ra parameter was 0.840±0.119 for the diagonal measurement and 0.855±0.147 for the horizontal one (see Fig. 4), the Rp criterion has shown the values of 1.95±0.04 and 2.45±0.04 (see Fig. 5).

The surface pattern of dental samples after rubbing the toothpaste with remineralizing compound in group III was visualized in the three-dimensional images as the predominance of colored areas of green and blue spectrum as compared to the moderately expressed red-colored areas (Fig. 8). The distribution of colors had intensive optical borders. The graphic representation of the surface of the enamel treated with the toothpaste, was observed as a wave-like line, in which foci of smoothened peak profile was alternating with the peak-like ones (Fig. 9). The values of roughness were the following: Ra 0.966±0.256 (diagonal measurement) and 1.281±0.586 (horizontal measurement) (see Fig. 4), while the height variation (Rp) was 2.21±0.86 and 2.49±0.41, respectively (see Fig. 5).

In group IV, after processing with the toothpaste having a remineralizing effect and after an addition of vitamin D (1000 IU per 100 ml), the three-dimensional images of the surface looked structurized, without any

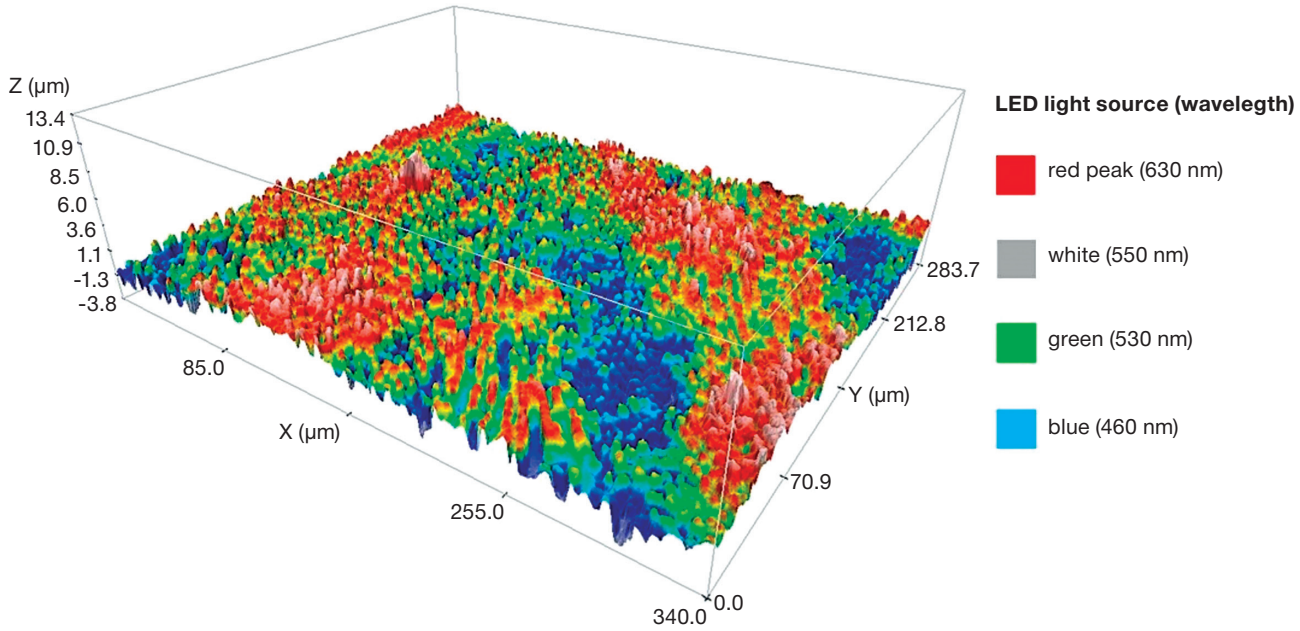

Fig. 6. Three-dimensional image of the dental enamel surface sample from group II.

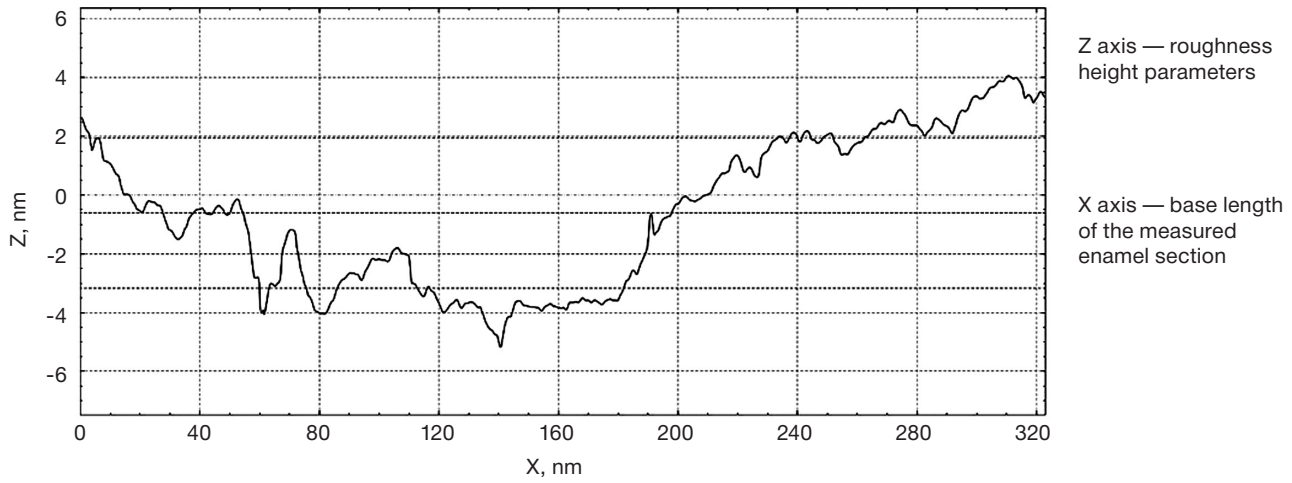

Fig. 7. Enamel surface profile of the sample from group II.

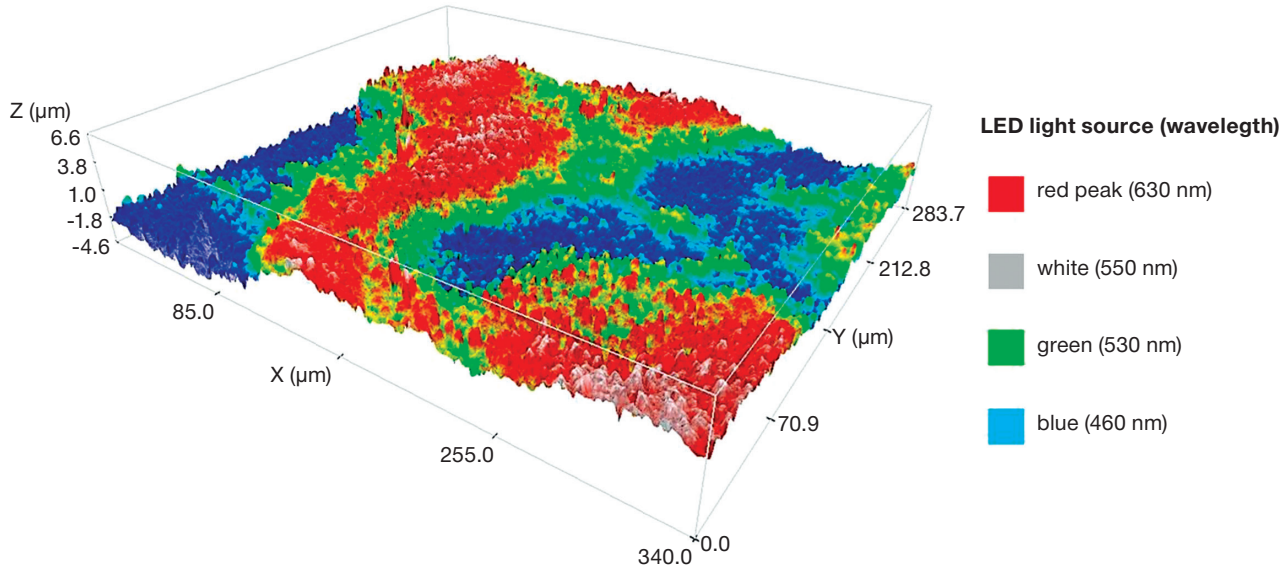

Fig. 8. Three-dimensional image of the dental enamel surface sample from group III.

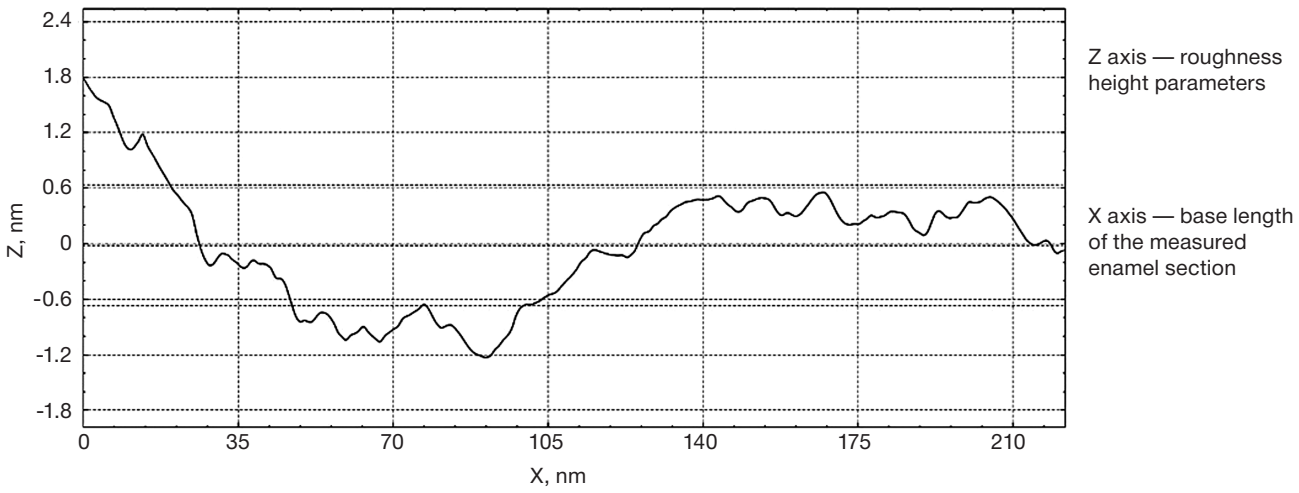

Fig. 9. Enamel surface profile of the sample from group III.

sharp peaks or valleys, also having a clear geometry of colored zones (Fig. 10). The profile graph did not have a peak-like gradient of graphic height, while the enamel surface has gained quite a smooth pattern with no signs of porous structure (Fig. 11). The roughness parameter Ra had the following values: diagonal measurement 3.482±0.158, horizontal - 3.568±0.476, Rp — 4.67±0.74 and 4.87±0.98, respectively (see Fig. 4, 5).

DISCUSSION

In all the groups, upon analyzing the results of measurements at the horizontal and diagonal directions, we have obtained the parameter values with no significant difference, which indicated the significance of data measured for the surface of the object having a volumetric non-linear shape — the equatorial zone of the contact surface of the tooth.

In patients with homozygous polymorphism (A/A) in the VDR gene, when evaluating the results of confocal profilometry, we have found that in group II (teeth contained in the solution of artificial saliva and vitamin D), changes have developed in the roughness of the enamel surface of the extracted teeth. An elevation of the values for the parameters Ra (1.4-fold; p=0.01) and Rp (2-fold; p=0.01) comparing to the group I (control) indicated the smoothness of the surface profile (see Fig. 4, 5). In the three-dimensional images, the additionally visualized findings included an enlargement of the areas colored green and blue (see Fig. 6). It can be suggested that this transformation

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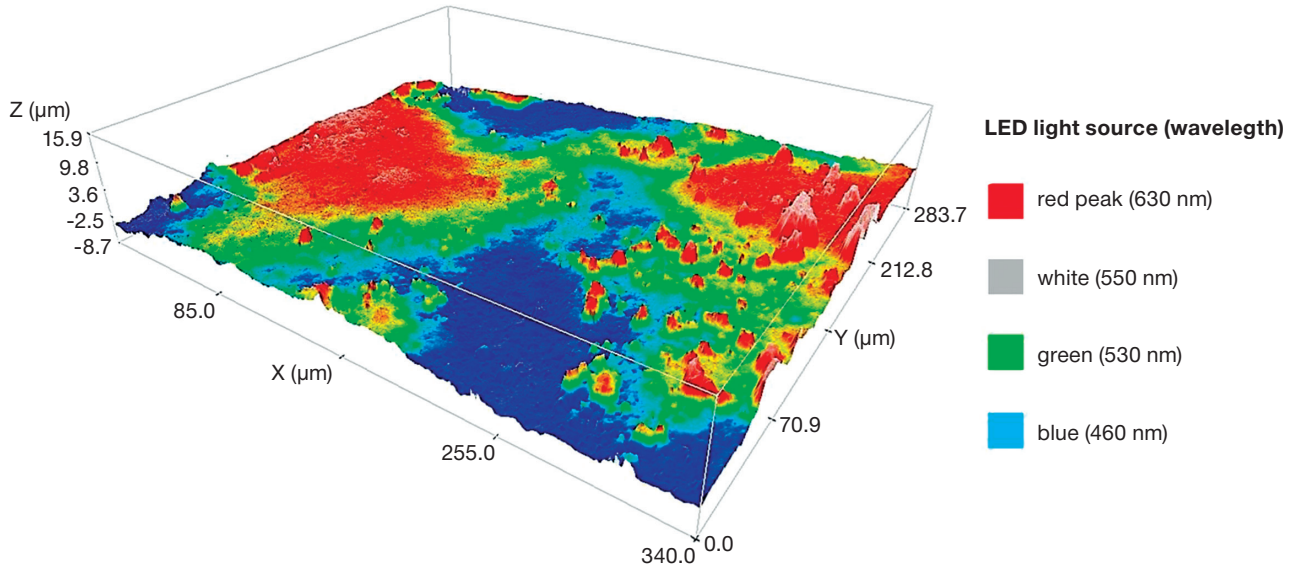

Fig. 10. Three-dimensional image of the dental enamel surface sample from group IV.

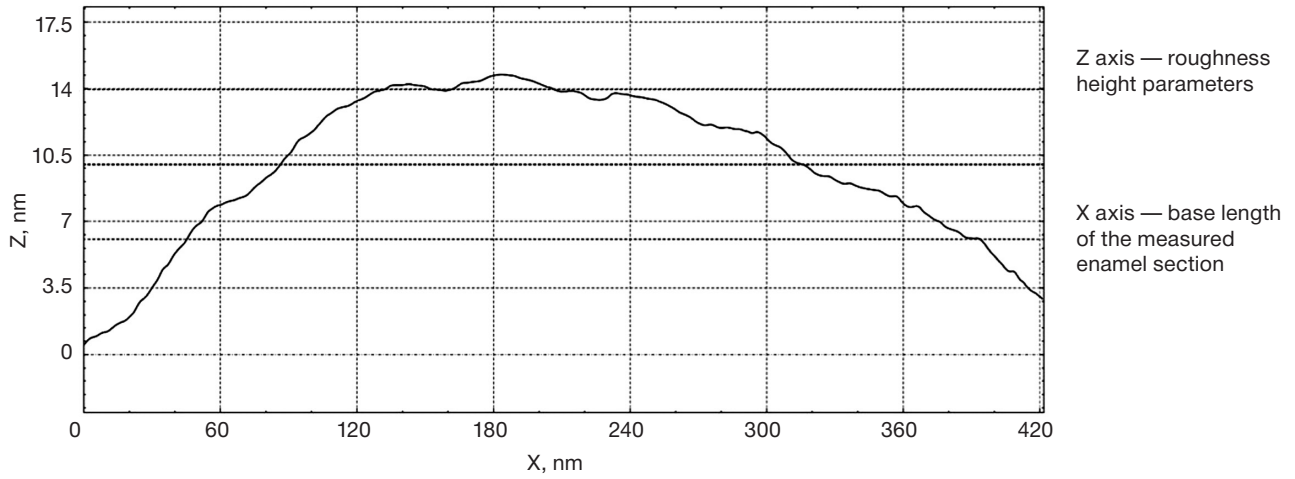

Fig. 11. Enamel surface profile of the sample from group IV.

of the enamel surface is related to the formation of mineralization zones due to the sedimentation of calcium-phosphate compounds from the artificial saliva solution in the presence of vitamin D.

The results in groups II (addition of cholecalciferol to the artificial saliva solution) and III (processing the enamel of the extracted teeth with remineralizing toothpaste) had significant changes in the roughness parameters comparing to the group I (control).

Upon comparing the Ra and Rp digital parameters between groups II and III, statistically insignificant differences were revealed: the presence of cholecalciferol in the artificial saliva or processing with remineralizing toothpaste have demonstrated similar digital values of roughness.

As for the samples from group IV (extracted teeth contained in the artificial saliva solution with vitamin D and processed with remineralizing toothpaste), they have demonstrated significant changes in the roughness of the enamel surface, which was confirmed by an increase in the values of Ra (8-fold; p=0.000001) and Rp (3-fold; p=0.00005) comparing to the control group I (see Fig. 4, 5). The obtained results are determined by the synergetic effects of vitamin D and microRepair microcrystals contained in the toothpaste.

This research points out that, among the individuals carrying the homozygous polymorphism (A/A) of the VDR gene, the combined use of remineralizing toothpaste and cholecalciferol promotes to the

improvement in the structure of the dental enamel and increases the level of its resistance.

CONCLUSION

In patients with homozygous polymorphism (A/A) of the VDR gene, upon containing the extracted impacted teeth in the solution of artificial saliva with further addition of cholecalciferol at a concentration of 1000 IU/100 ml and upon treating the enamel with remineralizing toothpaste, significant changes were shown for the Ra (p=0.000001) and Rp (p=0.00005) parameters. The increase of the values of these parameters results in a decrease in the pronounced roughness of the dental enamel, which is related to the formation (in the presence of vitamin D evenly distributed along the surface) of the homogeneous layer consisting of microRepair microcrystals.

The obtained results can be used for developing the program of preventing dental caries related to the impaired mineral metabolism caused by the homozygous polymorphism (A/A) of the VDR gene among the patients, which are in the high risk group.

ADDITIONAL INFORMATION

Author contributions. *S.N. Tikhonova:* collection and analysis of literary sources, conducting the experimental part of the study, preparing and writing the text of the article; *M.V. Kozlova:* idea and design of the study, surgical treatment of patients participating in the study, editing the text of the article; *E.A. Gorbatova:* analysis of literary sources, editing the text of the article. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics approval. All the patients enrolled into the research have signed the voluntary consents for the conduction of all the medical procedures, according to the Decree issued by the Ministry of Health and Social Development of the Russian Federation No. 390n dated 23.04.2012, in accordance with the Article 20 of the Federal Law No. 323 dated 21.11.2011. The research protocol was approved by the local Ethics Committee of the FSBI CPE CSMA, extract from the session protocol No. 1, dated 07.02.2023.

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Combined Physical Activity in the Prevention of Cardiovascular Diseases: From Physiological to Molecular Adaptation Mechanisms

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ABSTRACT

Physical activity is recognized as the most important non-medicinal tool for the prevention of cardiovascular diseases, however, the highest efficiency is demonstrated by the programs combining various types of physical load. The present review summarizes the current scientific data on the effects of combined physical activity, including the aerobic exercises of moderate and high intensity and the muscle strengthening exercises, as well as the ones affecting the system of cardiometabolic regulation. A disclosure is provided for the multi-level adaptation mechanisms, encompassing the physiological, vegetative, hormonal, molecular and epigenetic levels. It was justified that combined training modalities possess the synergetic effects, facilitating the decrease of blood pressure, the increase in the cardiac rhythm variability, the improvement of insulin sensitivity, the decrease of chronic inflammation and the activation of cardioprotective transcription programs. A detailed description was provided for the key molecular pathways participating in the adaptational response (AMP-activated protein kinase, mTOR, PGC-1α, autophagia and the unfolded protein response), as well as the role of exerkines — the signaling molecules produced in response to physical load. Special attention was paid to the epigenetic modifications, including the methylation of DNA, the regulation of microRNA and the telomere stability, as the mechanisms of long-term protection from the cardiovascular diseases. The data provided emphasizes the necessity of introducing the combined modalities of physical activity into the programs of individual and populational prevention. Besides, further research is required on the optimal combination of intensity, extent and patterns of physical load for various population categories for the purpose of maximizing the protective adaptation of the cardiovascular system.

Keywords: *physical activity; cardiovascular system; prevention; physiological adaptation; epigenetics; exerkines; mTOR; AMP-activated protein kinase; PGC-1α; variability of cardiac rhythm.*

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INTRODUCTION

Cardiovascular diseases (CVD) remain one of the leading causes of incapacitation, morbidity and premature mortality, representing one of the most severe problems for the modern public healthcare [1]. According to the data from the Global Burden of Disease research conducted in 2022, the global number of fatal outcomes related to CVD, has increased from 12.4 mln in 1990 to 19.8 mln in 2022 [2]. This dynamic change indicates the inextinguishable growth of the CVD burden, with this group of diseases continuing to take the first place among the causes of

Комбинированная физическая активность в профилактике сердечно-сосудистых заболеваний: от физиологических к молекулярным механизмам адаптации

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АННОТАЦИЯ

Физическая активность признана важнейшим немедикаментозным инструментом профилактики сердечно-сосудистых заболеваний, однако наибольшую эффективность демонстрируют программы, сочетающие различные виды физических нагрузок. В настоящем обзоре обобщены современные научные данные о влиянии комбинированной физической активности, включающей аэробные нагрузки умеренной и высокой интенсивности и упражнения на развитие мышечной силы, на систему кардиометаболической регуляции. Описаны мультиуровневые механизмы адаптации, охватывающие физиологические, вегетативные, гормональные, молекулярные и эпигенетические уровни. Обосновано, что комбинированные тренировочные режимы оказывают синергетическое действие, способствуя снижению артериального давления, повышению вариабельности сердечного ритма, улучшению инсулиночувствительности, снижению хронического воспаления и активации кардиопротективных транскрипционных программ. Детально рассматриваются ключевые молекулярные пути, участвующие в адаптационном ответе (AMPK, mTOR, PGC-1α, аутофагия, UPR), а также роль экзеркинов — сигнальных молекул, продуцируемых в ответ на физическую нагрузку. Отдельное внимание уделено эпигенетическим модификациям, включая метилирование ДНК, регуляцию микроРНК и теломерную стабильность, как механизмам долговременной защиты от сердечно-сосудистых заболеваний. Представленные данные подчёркивают необходимость внедрения комбинированных режимов физической активности в программы индивидуальной и популяционной профилактики. Кроме того, требуется дальнейшее изучение оптимального сочетания интенсивности, объёма и направленности физических нагрузок для различных категорий населения с целью максимизации адаптационных возможностей сердечно-сосудистой системы.

Ключевые слова: *физическая активность; сердечно-сосудистая система; профилактика; физиологическая адаптация; эпигенетика; экзеркины; mTOR; AMPK; PGC-1α; вариабельность сердечного ритма.*

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mortality and loss of working capacity in the Russian Federation [3].

Notably, the high incidence of CVD is observed not only in the countries with high income level: approximately 80% of all the fatal outcomes related to CVD are registered in the countries with low and medium income level, which emphasizes the omnitude and the multi-aspect nature of this epidemiological problem [4]. In Russia, from the middle of 60s of the past century, a growth was observed in the general mortality, especially the CVD-related one, unlike the stable decrease in the Western countries. The main factors of such growth became the urbanization, the alcoholization and the spreading of risk factors (increased blood pressure, smoking, hypercholesterolemia). From 2003, the mortality was beginning to decrease, mainly due to the decreased spreading of risk factors and improving the accessibility and the quality of medical aid, however, Russia still remains a country with high CVD-related mortality rates with significant regional and gender-associated differences [5].

Cardiovascular diseases develop under the influence of a whole spectrum of complex factors, among which, special place is taken by the behavioral and the modifiable determinants, including the insufficient physical activity, the non-balanced nutrition, chronic stress, abnormal sleep modes and the effects of unfavorable factors from the environment. Insufficient physical activity, in particular, is recognized as one of the key global risk factors of CVD, associated with significant increase of the relative risk of general and cardiovascular mortality [6].

According to the actual global review [7], the incidence of insufficient levels of physical activity is 26.3% of the general population. This problem takes the central place in the list of modifiable behavioral risk factors, according to the recommendations from the American Heart Association (AHA), set forth in the Life's Essential 8 concept, along with the control of blood pressure, lipid profile, glucose level, normalization of the body weight and smoking cessation.

Despite the recognized efficiency of physical activity in the context of preventing CVD, there still remains a disputable issue on the optimal distribution and combination of various types of physical load — moderate, intensive or muscle strength oriented — from the point of view of the cardioprotection. In one of the most representative cohort studies based on the data from the National Health Interview Survey (NHIS) [8], it was found that the best decrease in the risk of cardiovascular mortality was observed in cases of combined use of all the three types of physical activity. This emphasizes the necessity of adding the strength exercises to the aerobic activity of moderate and high intensity as a part of CVD prevention strategy.

Similar conclusions were reported by M. Hollings et al. [9], pointing out the progressive muscular exercises promote to the improvement of cardiorespiratory stamina — one of the most significant predictors of survival rate in patients with ischemic heart disease. Thus, multicomponent physical training sessions including the aerobic and strength exercises play a key role in primary prophylaxis and decreasing the global CVD burden.

We have arranged a comprehensive analysis of the existing data on the effects of various types of physical activity (moderate and high intensity aerobic, as well as muscle-building exercises) on the cardiovascular wellness with an accent to the mechanisms of their action in a context of primary prevention of cardiovascular diseases.

Methodology of searching and selecting the research works

The analysis included the scientific literature published from 2000 until 2024 in the international databases — PubMed, Scopus, Web of Science, as well as at the Google Scholar and eLIBRARY platforms.

To select the relevant sources, we used the following key words and logical operators: "physical activity" AND "cardiovascular adaptation", "combined exercise" AND "prevention of cardiovascular disease", "molecular mechanisms" OR "epigenetics" AND "exercise", "autonomic nervous system" AND "training", "exerkines" OR "PGC-1α" OR "AMPK" OR "mTOR".

From the initial sample of more than 600 publications, a total of 72 sources were selected, reflecting the most significant and recent data on the topic.

A REVIEW OF THE ADVANTAGES OF COMBINED PHYSICAL ACTIVITY COMPARING TO THE ISOLATED EXERCISE PATTERNS

Modern cardiology and preventive medicine are more and more actively investigating physical activity as an integral part of the combined prevention of CVD. The systematic participation in physical activity is recognized as one of the most effective and accessible instruments of modifying the risk factors, associated with CVD and premature mortality. However, for achieving the maximal therapeutic and preventive effect, more and more attention is paid not only to the

extent and the regularity of physical activity, but also to its structure, intensity and diversity.

According to the recommendations on the primary prophylaxis of CVD, presented in 2019 [10], the adults are recommended to devote not less than 150 minutes a week to physical activity of moderate intensity, or 75 minutes for high intensity, or their equivalent combination. These recommendations, being aimed at decreasing the risk of developing CVD, reflect the universal approach to the prevention, however, they insufficiently enlighten on the proven benefits of supplementing the training program with exercises aimed at strengthening the skeletal muscles. According to the number of epidemiological and interventional researches, specifically the combined model of physical activity, including the aerobic and strengthening components, is associated with the most significant decrease in the risk of both the cardiovascular and the total mortality [8, 11].

Physiological mechanisms lying at the roots of such effects are various. Moderate physical activity is generally associated with an increase of the total energy usage, with the normalization of the lipid and glycemic profile, with the decrease in the quantity of visceral fat and with the improvement of the arterial tone [12], while the highly intensive load significantly effects the development of cardiorespiratory stamina, which is an independent predictor of survival rate, regardless of the gender, the age, the body mass index and ethnicity [13, 14].

The clinical and populational research works confirm that combining the exercises of various intensity provides a synergetic effect. For example, even moderate physical activity promotes to the decrease of cardiometabolic risk, however, its combination with intensive physical exercises demonstrates significantly more pronounced decrease in the CVD mortality [15]. Moreover, the benefit remains even in case of a minimal life style modification: for example, when changing the sedentary behavior to mild activity during the day combined with regular sessions of aerobic exercises [16].

The meta-analysis of interventional studies [17] has shown that active physical load decreases the levels of inflammatory markers, normalizes the parameters of cardiac rhythm variability and promotes to the decrease of blood pressure. These effects are especially pronounced when combining the aerobic and strength-building exercises, while the strength exercises itself promote to the improvement of metabolic homeostasis, to the decrease of insulin resistance and to the increase of muscle mass, which is of major importance at the elderly age. For this age group, the additionally recommended are the balance and coordination exercises, promoting to decreasing the risk of falling and concomitant incapacitation [18].

From the point of view of pathophysiology, the intensity of loading directly affects the degree of intensity of the adaptational processes. The randomized research works have found that intensive physical activity promotes to more significant increase in the heart rate and lactate level, while the moderate load shows a stable effect on the vascular reactivity and microcirculatory network. Besides, physical activity of various intensity can variously affect the expression of microRNA, participating in re-modeling of vessels and in the arteriogenesis, which opens new perspectives in a context of molecular medicine [19, 20].

Special attention should be paid to the data obtained using the accelerometry method, indicating that changing even 5 minutes of sedentary lifestyle to high intensity activity may lead to the improvement of body constitution, to the increase in the level of fat-free body weight and to the improvement of cardiorespiratory functions, especially in children and adolescents [21]. In younger adults with excessive body weight, it was proven that moderate and high-intensity physical activity is more effective than the mild one in terms of improving the cardiometabolic wellness [22]. At the same time, it should be taken into account that, for the majority of the population, especially for individuals from the older age group, high-intensity exercises can be less acceptable, which is why specifically the reasonable combination of exercises of various intensity and patterns is the most practicable strategy.

As shown by the comparative research works, moderate and intensive exercises similarly affect the decrease of the total and cardiovascular mortality, however, specifically the intensive physical activity, to a greater extent, is associated with a decrease in the oncological mortality [23]. This additionally underlines the multisystemic effect of physical activity and the topicality of the individualized approach to compiling the training programs.

The combined training models demonstrate not only the preventive, but also the therapeutic potential. A cohort study based on the data from the National Health Interview Survey in the USA (NHIS) [8] has demonstrated that the most significant decrease of cardiovascular mortality was observed among the individuals, combining aerobic exercises of various intensity with strength exercises. Detailed results were obtained during the controlled clinical research [24], where the 12-weeks program,

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including the cardio- and strength-related components, has lead to a significant decrease in the values of heart rate at rest, the blood pressure, the body weight and the fat mass, as well as to the improvement of maximal oxygen consumption (VO_2 max).

Thus, the necessity of revising the existing guidelines becomes evident with an accent to structural diversity of physical activity. The inclusion of the provisions concerning the significance of combined physical activity into the official recommendations shall allow for increasing the efficiency of both the primary and the secondary prevention of CVD, as well as the degree of patients' compliance to healthy lifestyle. The formation of a holistic approach based on the integration of various types and levels of physical activity must become an integral part of the modern programs of preventing and rehabilitation for CVD.

Combined physical activity (aerobic+strength-building) provides more intensive cardiometabolic and preventive effects comparing to the isolated types of exercises. Combining various types of exercises promotes to synergetic effects on the cardiovascular system, decreasing the mortality and improving physiological adaptation.

HORMONAL ADAPTATION TO PHYSICAL ACTIVITY: METABOLIC AND ENDOCRINE EFFECTS

Physical activity causes a number of systemic positive effects on the metabolic health of the human, largely thanks to its regulating effects on the hormonal homeostasis [25]. One of the key endocrine effects of the regular motor activity is the increase in the sensitivity of the target tissues to insulin, especially when performing exercises aimed at developing muscle strength and increasing the muscle mass [26].

It was found that regular physical activity promotes to the modulation of the transduction of insulin signals in the skeletal muscles [27], stimulating the biogenesis of the mitochondria and the remodeling of muscle tissue by means of the activation of a number of molecular signaling pathways, including the endothelial nitric oxide synthase (eNOS), the peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) and the mitofusin [28–30]. These mechanisms play the key role in increasing the oxidative capabilities of the muscles, improving both the metabolic flexibility and the insulin sensitivity [31].

Physiologically, eNOS increases the perfusion of tissues, sensitive to insulin, such as the myocardium and the skeletal muscles, by this enhancing the delivery of glucose and other metabolites [32]. Moreover, during the randomized controlled research, it was shown that 10-weeks strength-building training course promotes to the improvement of localizing the neuronal nitric oxide synthase (nNOS) in the skeletal muscles, which is critically important for the effective vasoregulation [33].

Physical activity also activates the expression and the translocation of GLUT4 (glucose transporter type 4), providing an increased uptake of glucose by muscle cells and facilitating its accumulation as glycogen [34, 35]. Even a single training session (for example, 45–60 minutes of riding a bicycle at 60–70% of VO_2 max) induces the translocation of GLUT4 to the cellular membrane in the skeletal muscles in patients with type 2 diabetes mellitus [36]. This mechanism forms the basis of improving glycemic control in the given category of individuals.

Special significance is gained by physical activity aimed at developing the muscle strength, for it promotes to the increase of muscle mass — the main glucose depot in the organism — and to the improvement of its metabolic quality [37, 38]. Thus, only two sessions of progressive strength-building sessions a week, even with no additional interventions in the diet, significantly improve the sensitivity to insulin, decrease the fasting glucose level and reduce visceral obesity in elderly men with type 2 diabetes mellitus [39].

The efficiency of physical training is also observed in persons with pre-diabetes, as well as among those who are in the high-risk group in terms of developing type 2 diabetes. The network meta-analysis [40], including the data from 13 randomized controlled studies, has shown that 12-weeks programs of physical activity combining aerobic and strength-building exercises significantly decrease the level of glycated hemoglobin, (HbA1c) in persons with impaired glucose tolerance. Moreover, regular physical activity, both combined with controlling the body weight and in the autonomous mode, was proven to promote the prevention or significant delay of the manifestation of type 2 diabetes mellitus [41, 42].

Special attention deserves the role of catecholamines — adrenalin and noradrenalin — in the regulation of the metabolism and the cardiovascular functions in response to physical load. These hormones are synthesized by the medullary substance of the adrenal glands and they are released in response to acute stress, including physical activity [43]. The stimulation of β-adrenoreceptors with catecholamines increases the rate and the strength of heart contractions, dilates the arterioles in the skeletal muscles and enhances the accessibility of metabolic substrates [44].

Catecholamines also modulate the functions of the immune system, in particular, the activity of T- and B-lymphocytes, the synthesis of cytokines and antibodies, which is of significant meaning both for the immuno-metabolic regulation and for systemic anti-inflammatory response [45]. Besides, they provide the mobilization of fatty acids and glucose, required for supporting the energy needs of the skeletal muscles during the long-term physical activity [45, 46].

The level of catecholamines production directly correlates with the level of physical training: among the individuals training the stamina, the findings include higher capabilities to adrenalin secretion, which was denominated as the phenomenon of "sports-related adrenal cortical hyperplasia" [44]. Moreover, regular physical activity induces the adaptation of the sympathoadrenal system, increasing the sensitivity of peripheral adrenoreceptors and the efficiency of response reactions to physical load [47], which additionally contributes to the improvement of the regulation of blood pressure, of glycemic control and of the lipid metabolism. Table 1 summarizes the main hormonal effects of physical activity [26–47].

Thus, hormonal adaptations induced by regular physical activity, are implemented by means of the multi-level mechanisms — from the molecular activation of insulin-dependent signaling pathways to systemic modulation of catecholamine activity and vascular regulation. These processes not only promote to the improvement of metabolic and hormonal status, but also play the key role in the prevention and control of chronic non-infectious diseases, including type 2 diabetes mellitus and CVD. Thus, the integration of aerobic and strength-building components of physical activity into the structure of everyday activities is a justified strategy of preserving the hormonal balance and metabolic wellness at all the stages of life.

Regular physical activity promotes to the improvement of hormonal background and metabolic wellness due to the increase of sensitivity to insulin and due to the activation of anabolic signaling pathways. These adaptations decrease the risk of developing

Table 1

Hormonal effects of physical activity

Hormonal effect	Mechanism of action	Type of physical activity	Source
Increasing the sensitivity to insulin	Activation of signaling pathways in the muscles (eNOS, PGC-1α, mitofusin); stimulation of biogenesis in mitochondria	Strength-building, aerobic	[26–31]
Improvement of circulation in the target organs	Increased activity of eNOS and nNOS	Aerobic, strength-building	[32, 33]
Translocation of GLUT4, increased glucose usage	Increased expression of GLUT4 and its translocation to the cell membrane	Aerobic, especially with high intensity	[34–36]
Increasing the muscle mass and metabolic activity of the muscles	Growth of muscle mass, increased the reserves for glucose utilization	Strength-building	[37–39]
Decreased insulin resistance in pre-diabetic individuals	Combined adaptation: decrease of fat mass, improvement of HbA1c	Combined (aerobic+ strength-building)	[40]
Prophylaxis of type 2 diabetes among the persons of the risk group	Physical load, decrease in the body weight, dietary intervention	Aerobic, strength-building	[41, 42]
Stimulation of the secretion of catecholamines	Activation of the adrenal glands and of the sympathetic nervous system in response to physical load	Intensive	[43–45]
Improvement of the functions in the cardiovascular system via the β-receptors	Increased heart rate, force of contractions, vasodilation	Aerobic, intervallic	[44]
Increased lipolysis and oxidation of fats	Increased catecholamine response; mobilization of energy substrates	Intensive	[45, 46]
Increasing the sensitivity of the adrenoreceptors	Long-term adaptation of the sympathoadrenal system	Regular aerobic and strength-building	[47]

Note. eNOS/nNOS — endothelial/neuronal nitrogen oxide synthase; PGC-1α — peroxisome proliferator-activated receptor-gamma coactivator-1α, regulator of mitochondrial biogenesis; GLUT4 — glucose transporter, type 4; HbA1c — glycosylated hemoglobin.

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metabolic syndrome and type 2 diabetes mellitus, especially when adding the strength-building exercises.

VEGETATIVE ADAPTATION TO REGULAR PHYSICAL ACTIVITY

Physical activity acts as an important stimulus for vegetative restructurisation, facilitating the development of stable neurophysiological changes, directed at increasing the efficiency of cardiovascular, metabolic and respiratory regulation. The adaptational processes in the vegetative nervous system play the key role in providing the homeostatic resistance of the organism to physical load of various intensity and duration.

The vegetative nervous system functions by means of two complementary segments — the sympathetic and the parasympathetic nervous systems. The activation of sympathetic nervous system initiates the so-called "fight or flight" reaction, accompanied by the acceleration of the cardiac rhythm, by elevation of blood pressure, by vasoconstriction and the decrease in the gastro-intestinal motor activity. On the contrary, the parasympathetic nervous system implements the reparative processes at rest, decreasing the frequency of heart contractions, facilitating the vasodilation, activating the secretion and the peristaltic motions in the digestive tract [48].

One of the key markers of vegetative tone used in clinical practice and sports medicine is the variability of the cardiac rhythm — the reflection of the degree of variation of the intervals between the consecutive heart contractions [49]. The low level of cardiac rhythm variability is significantly associated with elevated risk of sudden cardiac death, cardiac failure, hypertension and metabolic disorders, including type 2 diabetes mellitus.

One of the most important adaptations to regular physical activity, regardless of its modality, is the increase of parasympathetic tone with a simultaneous decrease in the activity of the sympathetic segment. These changes, occurring with preserved normal functions of the sinusal node, are due to the increased vagus modulation of the heart rate, facilitating its decrease at rest and the increase in the cardiac rhythm variability [50]. Such a parasympathetic shift is considered as the marker of high-level functional adaptation of the cardiovascular system and of decreasing the risk of developing CVD [51].

It was found that regular physical activity, especially of aerobic type, leads to an increase in the cardiac rhythm variability, both among the individuals with already diagnosed CVD and among the healthy individuals, which confirms its multi-purpose effects on the vegetative balance [52]. At the same time, neurophysiological adaptations occur also at the level of central regulation, in particular, in the rostral ventrolateral part of the medulla oblongata, playing the key role in the modulation of the sympathetic tone. These changes promote to the decrease of hyperactivation in the sympathetic nervous system, which is especially characteristic for persons with chronic stress and cardiometabolic disorders [53].

Moderate and intensive physical activity improves the sensitivity of the sympathetic nervous system to physiological stimuli, increasing the efficiency of responses upon physical loading due to more rational use of energy resources and due to the mobilization of catecholamines [54, 55], which is accompanied by an increase in the cardiac output, by vasodilation in the skeletal muscles, by the improvement of glucose transport and by an increased lipolysis.

Interestingly, but even at rest after regular aerobic exercises, a decrease is observed in the sympathetic activity, while when using the submaximal physical lead, a more energy efficient regulation of the vegetative is achieved, which indicates increase of the total vegetative efficiency [54, 55].

The vegetative adaptation is also characteristic for the strength-building exercises. Systematic exercises aimed at developing muscle strength, promote to the activation of the pituitary-hypothalamic-adrenal axis, providing a modulation of the production of cortisol, with the findings also including a decrease in its levels at rest and the suppression of the chronic inflammatory response [55]. The decrease in the levels of cortisol has a positive effect, for its chronic hyper-secretion correlates with the development of insulin resistance, arterial hypertension and atherogenic dyslipidemia — the main components of metabolic syndrome [56].

Regular muscle core strengthening exercises improve the sensitivity of β-adrenoreceptors in the skeletal muscles, enhancing the effect of catecholamines and facilitating the finer regulation of the vascular tone and metabolic processes [47]. Besides, strength-building activities promote to the increase in the cardiac rhythm variability, which indicates the restoration of the vegetative balance, similar to the one observed in cases of aerobic activities [57].

Thus, regardless of the type of physical activity, its regular conduction forms a favorable vegetative adaptation, including the increase of the vagus effects in the heart, the decrease of the sympathetic activation, the improvement of hormonal and neurovascular

regulation. The totality of such changes promotes to decreasing the risk of cardiometabolic disorders, to the improvement of the general stress resistance and to the increase of the functional reserves of the organism.

MOLECULAR ADAPTATION TO PHYSICAL ACTIVITY

Physical activity is a potent trigger for a wide spectrum of molecular adaptational processes, which mediate the positive effects of the motor activity in terms of general wellness. These processes include the activation of multiple intracellular signaling cascades, regulating the cellular homeostasis, energy metabolism, tissue plasticity and stress resistance. The special role in the modulation of the adaptive responses is played not only by the type and the intensity of physical load, but also by the accessibility of nutritive substrates, determining the metabolic direction of cellular regulation [58].

One of the key mechanisms activated in response to physical activity is the activation of autophagia — the evolutionary conservative pathway of disposal and reprocessing of organelles and proteins. Autophagia provides metabolic flexibility and maintenance of cellular homeostasis, playing the critical role in the adaptation to physiological stress related to muscle contractions [59]. Besides, mitochondrial biogenesis, autophagia and mitophagy (selective degradation of mitochondria) form the coordinated response in the tissues with high energy consumption, such as the skeletal muscles and the myocardium, facilitating the increase in the resistance to further load and the improvement of tissue metabolism [60].

In the settings of physical activity, a coordinated activation is observed in the mTORC1 (mechanistic target of rapamycin complex 1) and AMPK (5' adenosine monophosphate-activated protein kinase) pathways, which reflects the complex integration of anabolic and catabolic signals. Such a convergence of molecular cascades is especially important when combining the strength-building and aerobic exercises, explaining the phenomenon of the so-called "simultaneous training effect" [61].

At the level of transcriptional regulation, physical activity induces the expression of genes, controlling muscle hypertrophy, angiogenesis and remodeling of muscle fibers. It was noted that physical exercises activate both the myogenic and the angiogenic transcription programs, promoting to the complex tissue adaptation, directed at the optimization of delivering oxygen and substrates [62].

The most important role in regulating the cellular response to physical activity is played by the unfolded protein response (UPR), activated in the settings of increased synthetic load. This mechanism allows the cells to manage the stress in the endoplasmatic reticulum, maintaining proteostasis in the conditions of intensified metabolism [63].

The recognized central element of molecular adaptation to physical activity is the Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α (PGC-1α) — the key regulator of mitochondrial biogenesis. The activation of PGC-1α promotes to the increase in mitochondrial density, to the improvement of the oxidative capabilities of muscle cells and to the resistance to tiredness [64]. The PGC-1α regulation is also associated with the modulation of the expression of genes encoding the antioxidant enzymes, which is important in a context of protection against oxidative stress.

The molecular responses to physical activity demonstrate a complex and multicomponent pattern, which requires a comprehensive analysis. Understanding the integration of the AMPK, mTOR, MAPK (mitogen-activated protein kinases) and UPR signaling pathways along with the transcription factors, activated upon moderate and high intensity physical activity, is critically important for unveiling the mechanisms of cellular adaptation [65]. The mTOR pathway has demonstrated, along with the metabolic functions, an important role in regulating the neuroplasticity, the cognitive abilities and the structural re-organization of neuronal networks in the brain in response to physical load [66], which opens new perspectives of using physical activity as the non-medicinal mean of improving the cognitive status in cases of neurodegenerative and vascular diseases.

The regulation of the expression of genes sensitive to physical activity, including the epigenetic modification, remains an object of active research. Special interest is aroused by the exerkines — the signaling molecules produced by skeletal muscles in response to contractions and showing systemic endocrine-like effects. The exerkines are considered as potential therapeutic agents for cardiovascular, metabolic and neurodegenerative diseases [67].

Thus, physical activity initiates a wide spectrum of molecular mechanisms, promoting to the structurally functional remodeling of tissues, to the increase of metabolic efficiency and stress-resistance. The variety of adaptive responses confirms the necessity of personalized approach in selecting the type and the

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intensity of physical exercises for preventive purposes and for the correction of chronic diseases. The molecular mechanisms of adaptation to physical activity are provided in Table 2 [59–61, 63, 64, 66, 67]. Physical activity also stimulates the key molecular pathways (AMPK, mTOR, PGC-1α, autophagia), promoting to the improvement of the energy metabolism, stress resistance and tissue remodeling (Table 3) [61, 63, 64, 66, 67] — the processes lying in the foundation of metabolic flexibility and of the cardioprotective effect of working out.

EPIGENETIC ADAPTATIONS IN RESPONSE TO PHYSICAL ACTIVITY

Modern research works strongly confirm that regular physical activity provides a significant epigenetic effect, playing the key role in regulating the genetic expression without changing the primary DNA sequence. These molecular modifications promote to the long-term remodeling of cellular functions, forming the basis for stable improvement of the cardiometabolic profile and of the general physiological status.

Table 2

Molecular mechanisms of adaptation to physical activity

Molecular pathway	Main effects	Source
Autophagia	Removal of damaged organelles and proteins, maintaining the cellular homeostasis	[59]
Mitochondrial biogenesis	Increase in the number of mitochondria, improvement of oxidative metabolism	[60]
mTORC1	Stimulation of protein synthesis, muscle growth, participation in neuroplasticity	[61]
AMPK	Activation of catabolism, energy mobilization, stimulation of mitophagy	[61]
PGC-1α	Regulation of mitochondrial genes, antioxidant protection, angiogenesis	[64]
UPR (unfolded protein response)	Adaptation to metabolic stress, control of proteostasis	[63]
Exerkines	Secretion of myokines, systemic regulation of metabolism and vascular functions	[67]
mTOR and cognitive function	Memory improvement, neurogenesis, synaptic plasticity	[66]

Note. AMPK — AMP-activated protein kinase, the energy sensor in the cell, activated in the settings of energy deficit; mTORC1 — the main component of the mTOR signaling pathway, regulating the cell growth, protein synthesis and metabolism; PGC-1α — the main regulator of mitochondrial biogenesis and oxidative metabolism in the skeletal muscles; UPR — the response to unfolded proteins, a cellular mechanism of adaptation to stress in the endoplasmatic reticulum; exerkines — the common name for signaling molecules, including the myokines, excreted into systemic circulation in response to physical activity.

Table 3

The main signaling pathways of adaptation to physical activity

Signaling pathway	Activation conditions	Main effects	Source
AMPK	Physical load and energy deficit (increased levels of AMP/ATP)	Activation of catabolism, stimulation of mitophagy, enhanced oxidation of fats	[61]
mTOR	Sufficient energy status, especially after exercises	Stimulation of protein synthesis, growth of muscle mass, participation in neuroplasticity	[61, 66]
PGC-1α	Increased metabolic activity and aerobic exercises	Increased mitochondrial biogenesis, angiogenesis, antioxidant protection	[64]
UPR	Stress in the EPR after intensive workout intensive	Maintaining the proteostasis and adaptation to metabolic stress	[63]
Exerkines	Contraction of skeletal muscles	Systemic regulation of metabolism, vascular function, anti-inflammatory effects	[67]

Note. AMPK — AMP-activated protein kinase (energy sensor of the cell); mTOR — the mechanistic target of rapamycin, regulating the growth and the metabolism; PGC-1α — peroxisome proliferator-activated receptor-gamma coactivator-1α, regulator of mitochondrial biogenesis; UPR — unfolded protein response, mechanism of controlling the proteostasis in the EPR after stress; exerkines — signaling molecules excreted by skeletal muscles in response to the contraction; EPR — endoplasmic reticulum.

The epigenetic mechanisms induced by physical activity include the methylation of DNA, the post-translational modifications of histones, the changes within the structure of the chromatin, as well as the regulation of the expression of non-coding RNA, including the microRNA and the long non-coding RNA [68]. These processes promote the activation of protective transcriptional programs aimed at the suppression of inflammatory and proliferative signals, which is of special importance in the prevention of such chronic diseases as atherosclerosis, type 2 diabetes, oncological and neurodegenerative disorders [69].

Physical activity, especially when performed on a regular basis, induces the stable epigenetic remodeling in the cells of the cardiovascular system. These modifications promote to the suppression of atherogenic genes, to decreasing the expression of pro-inflammatory cytokines, to the improvement of endothelial functions and to the enhancement of antioxidant protection [68]. Thus, the epigenetic regulation is considered as one of the central mechanisms, mediating the cardioprotective effects of physical activity.

Data are being accumulated that show that intensive physical activity is capable of preventing DNA damage, of modulating the expression of genes controlling the telomere length and slowing down the epigenetic aging of the organism [70]. These effects are in part caused by the stabilization of methylation in the promotor areas of the genes participating in the regulation of cellular proliferation and apoptosis.

Special interest has the phenomenon of transgenerational epigenetic transition: according to the latest data, physical activity of the parents can affect the epigenetic markers in the germinal cells and, respectively, the expression of genes in the progeny [71]. These changes induced by favorable environmental factors (including the physical load), can be transitioned to the next generations, providing an inheritable resistance to metabolic disorders, cardiovascular and oncology diseases. Such an inter-generational transfer of adaptive phenotypes gives the physical activity the status of not only individual, but also the potentially inter-generational preventive instrument.

Despite the progress in studying the molecular biology of adaptation to physical activity, the insufficiently clear issue is the degree of participation of various types of activity (aerobic, strength-building, intervallic) in the modulation of specific epigenetic targets, however, the aggregate data indicate that each type of physical activity is capable of inducing a unique epigenetic effect, regulating the specific cascades of transcriptional and post-transcriptional changes [72].

Thus, physical activity represents a potent exogenous factor forming a long-term epigenetic remodeling at the level of separate cells, tissues and the organism in general. These changes form the basis of not only the short-term functional adaptation, but also the long-term protection from chronic diseases, facilitating the increase in life expectancy and improving its quality.

Physical activity induces stable epigenetic changes, including the methylation of DNA, modifications of histones and regulation of the microRNA, which promotes to the suppression of inflammation and slowing down the ageing process. These effects provide a long-term protection against cardiovascular and metabolic diseases, also capable of being transferred to the progeny. The epigenetic mechanisms of adaptation to physical activity are provided in Table 4 [68, 70, 71].

CONCLUSION

The present review summarizes the accumulated scientific data supporting the high efficiency of combined physical activity, including the aerobic exercises of moderate and high intensity combined with the exercises aimed at improving muscle strength. Such a multicomponent strategy demonstrates significant superiority over the isolated types of physical activity by the spectrum of positive physiological adaptations, especially in terms of the cardiovascular system.

Systematic implementation of various forms of physical activity allows for achieving a synergetic effect, expressed as an increase in the cardiorespiratory stamina, improvement of neurovegetative balance, metabolic resistance and decreased inflammatory background. These adaptations play the key role in decreasing the risk of developing cardiovascular diseases and increasing the quality of life in various age groups and clinical groups.

The obtained results are of major importance both for developing the personalized preventive programs and for compiling the populational strategies of improving the wellness. The integration of various types of physical activity into everyday practice shall be considered a central element of combined interventions in the field of public healthcare and cardiology prevention.

Taking into consideration the high clinical and social significance of the data compiled in the present review, it is deemed appropriate to draw the attention of the professional medical communities and of the persons

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Table 4

Epigenetic mechanisms of adaptation to physical activity

Epigenetic mechanism	Mechanism description	Physiological effects	Source
Methylation of DNA	Addition of methyl groups to cytosine residues in the promotor areas of the genes	Decreased expression of pro-inflammatory and atherogenic genes, slowing down ageing	[68, 70]
Modification of histones	Acetylation, methylation and other post-translational changes in the histones	Remodeling of chromatin, regulation of DNA accessibility for transcription	[68]
Non-coding RNA (miRNA, lncRNA)	Regulation of transcription and translation by means of microRNA and long non-coding RNA	Decreased inflammation; regulation of angiogenesis, metabolism	[68, 71]
Methylation of RNA	Changes at the mRNA level, affecting the stability and translation	Plasticity of cell response to work-out, increased adaptation	[68]
Telomere regulation	Preserving the telomere length, preventing the chromosomal instability	Slower cell ageing, genome protection	[70]
Transgenerational epigenetics	Inheritable changes in gene expression without changing the DNA sequence	Transfer disease resistance to progeny	[71]

Note. miRNA (microRNA) — microRNA, non-coding RNA (regulating the expression of genes at the post-transcription level; lncRNA — long non-coding RNA (taking part in the regulation of transcription and chromatin organization); mRNA (messenger RNA) — matrix RNA (transfers the information on the protein sequence from the DNA to the ribosomes).

responsible for managerial decisions, to the necessity of encouraging and implementing the multi-level models of physical activity in various contexts — from individual prevention to population-scale programs.

The promising direction of further research is the clarification of the optimal ratio of intensity, volume and structural composition of various types of physical activity with taking into consideration the gender, the age, the functional status and the presence of comorbidities for the maximization of the preventive potential with regard to the cardiovascular outcomes.

As for the practical aspect, the obtained data underline the necessity of recommending combined physical activity for the general population: patients should combine aerobic exercises (of moderate and high intensity) with strength-building sessions not less frequent than two times a week, while the physicians should personalize the recommendations with taking into consideration the age, the general fitness level and the presence of chronic diseases, using the objective adaptation markers (for example, variability of cardiac rhythm and carbohydrate metabolism parameters) for monitoring the efficiency of the intervention.

ADDITIONAL INFORMATION

Author contributions. *A.R. Magomedov:* conceptualization and study design, overall scientific supervision, manuscript editing, and approval of the final version of the article; *P.V. Rykova:* methodology, data acquisition and systematization, drafting sections on physiological and molecular adaptation, and contribution to manuscript writing; *B.A. Anokhin:* literature analysis, contribution to sections on hormonal and epigenetic adaptation, and reference formatting; *A.Kh. Melikian:* preparation of tables and illustrative materials, formatting of bibliographic references; *M.A. Agaronian*, *A.G. Sarkisyan*, *E.S. Shimko:* analytical data processing, drafting of the “Introduction” and “Conclusion” sections; *A.Yu. Yusupova*, *E.R. Irgalieva:* scientific editing and critical manuscript review, verification of factual accuracy; *E.M. Bokova:* preparation of the English version of the abstract, keywords, and article title translation; *R.S. Mokaev*, *D.V. Leonova*, *A.Sh. Kendzhametov*: technical support with document formatting, verification of references, and coordination of the final manuscript version. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Multi-Channel Functional Electrostimulation: The Method of Restoring the Walking Function in Patients with a Past History of Acute Cerebrovascular Event

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ABSTRACT

Multi-channel functional electrostimulation (MFES) represents a promising method for the rehabilitation of post-stroke patients, aimed at restoring the walking function in various periods after an acute cerebrovascular event. The review systematizes the modern concepts of using the MFES in patients with the consequences of cerebral stroke, analyzing the technical parameters of stimulation, the methodical approaches to conducting the procedures and the clinical efficiency of the method. The analysis of literature data demonstrates significant variability of MFES protocols: the stimulation frequency varies from 20 to 100 Hz, the duration of the procedure ranges from 15 to 60 minutes, the treatment course can last from 3 to 30 weeks. The main targets of stimulation are the four groups of muscles in the lower limbs — the anterior tibial muscle, the plantar flexors, the quadriceps muscle of thigh and the group of muscles on the posterior surface of thigh. The synchronization of stimulation with the walking cycle is conducted predominantly by means of contact sensors, accelerometers and electromyographic signals; modern developments include the inertial systems and the machine learning algorithms. The review presents a combined analysis of the technical aspects of MFES from the point of view of staging of motor learning and individualization of the stimulation parameters. Special attention was paid to the integration of MFES with the robotic devices, including the exoskeletons, which represents a new trend in rehabilitation. Along with the absence of the unified criteria for choosing the stimulation parameters, it is worth noting that there is a necessity of differentiated approach depending on the type of motor disorders, on the duration of the disease and on the cognitive capabilities of the patient. The analysis presented justifies the necessity of developing personalized MFES protocols and arranging a large-scale research for optimizing the stimulation parameters in the rehabilitation of post-stroke patients.

Keywords: *multichannel functional electrical stimulation; stroke rehabilitation; gait; motor recovery.*

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BACKGROUND

Currently, one of the main objectives of early rehabilitation among the patients after an acute cerebrovascular event (CVA) is restoring the functions of walking without assistance [1, 2].

It is known that, already at the early stage after the CVA, hemiparesis typically develops, which is associated with gait abnormalities caused by the developing asymmetry both in the spatial and the timing parameters of the step cycle, which significantly restricts the ability of unassisted walking, also affecting the balance control, leading to the increased risk of falling [3, 4].

According to the data from the research on the biomechanics of walking, the gait parameters in patients with a past episode of stroke show typical impairment patterns of this function [5–8]. The patients after a cerebral stroke have lower walking speed with their gait being asymmetrical by many parameters, the stance phase on the paretic side is significantly shorter than the one on the contralateral side. Significantly less is the amplitude of motions in

Многоканальная функциональная электростимуляция: метод восстановления функции ходьбы у пациентов, перенёсших острое нарушение мозгового кровообращения

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АННОТАЦИЯ

Многоканальная функциональная электростимуляция (МФЭС) представляет собой перспективный метод реабилитации постинсультных больных, направленный на восстановление функции ходьбы в различные периоды после острого нарушения мозгового кровообращения. Обзор систематизирует современные представления о применении МФЭС у пациентов с последствиями церебрального инсульта, анализируя технические параметры стимуляции, методические подходы к проведению процедур и клиническую эффективность метода. Анализ литературных данных демонстрирует значительную вариабельность протоколов МФЭС: частота стимуляции варьирует от 20 до 100 Гц, длительность процедур составляет от 15 до 60 минут, курс лечения может продолжаться от 3 до 30 недель. Основными мишенями воздействия являются четыре группы мышц нижних конечностей — передняя большеберцовая мышца, подошвенные сгибатели, четырёхглавая мышца бедра и группа мышц задней поверхности бедра. Синхронизация стимуляции с циклом ходьбы осуществляется преимущественно посредством контактных датчиков, акселерометров и электромиографических сигналов; современные разработки включают инерциальные системы навигации и алгоритмы машинного обучения. В обзоре представлен комплексный анализ технических аспектов МФЭС с позиций этапности двигательного обучения и индивидуализации параметров стимуляции. Особое внимание уделено интеграции МФЭС с робототехническими устройствами, включая экзоскелеты, что представляет новое направление в реабилитации. Наряду с отсутствием единых критериев выбора параметров стимуляции следует отметить необходимость дифференцированного подхода в зависимости от типа двигательных нарушений, периода заболевания и когнитивных возможностей пациента. Представленный анализ обосновывает необходимость разработки персонализированных протоколов МФЭС и проведения масштабных исследований для оптимизации параметров стимуляции в реабилитации постинсультных больных.

Ключевые слова: *функциональная электростимуляция; реабилитация; инсульт; ходьба.*

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the joints on the paretic side [5–7]. Electromyographic (EMG) examinations of the muscles in the lower limbs in hemiparetic patients show the changes in the electric activity of muscles, which manifests by the absence or by the decrease in the amplitudes and by the presence of pre-term or delayed muscle activity peaks [8].

One of the variants of restoring the walking function in general and of achieving the walking symmetry in particular is the method of repeated teaching the motor skills, for which, the high-intensity repeating specific training sessions are necessary at the early period of rehabilitation after the CVA [9]. One of the promising methods of restoring the walking function is

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the method of functional electrostimulation of muscles (FES)[1]. Specifically, this context of fulfilling a certain functional task, as it was initially described by the authors of the method — J.H. Moe and H.W. Post [10], makes this field topical in modern rehabilitation. In particular, FES is used for reproducing the example of automatic activation of muscles in the lower limbs during the process of restoring the walking function [11], and specifically for this purpose, the artificial external excitation of muscles with electric current is used.

The mechanism of FES efficiency, nevertheless, remains unclear. For example, in the research by G.F. Santos et al. [12], it was found that FES improves walking in patients with a foot drop syndrome, with this, the basis of this effect is not evident.

The MFES method was assessed as promising in terms of restoring the walking function, beginning from the early rehabilitation period after the cerebral stroke and up to the onset of the residual neurological deficit period. Thus, at the early recovery period, when the pathological gait is still at the development phase, the use of MFES, evidently can be associated with higher efficiency.

The aim of this research is exploring the possibilities of MFES for restoring the walking functions in patients with a past episode of cerebral stroke.

Methodology of searching the literature sources

For searching the literature sources, the PubMed, eLibrary and Google Scholar databases were used. The search with a depth of up to 10 years was using the following key words and their combinations: “stroke”, “CVA”, “rehabilitation”, “walking”, “multi-channel functional electrostimulation”, “stroke”, “rehabilitation”, “gait”, “multichannel functional electrical stimulation”. The inclusion criteria for the analysis were the following: the analytical reviews, the clinical and experimental research, the recommendations from the scientific communities, the full texts of articles in Russian or in English.

Exclusion criteria: clinical cases; research works devoted to the foot drop syndrome; the ones where stimulation was applied to only one muscle; the use of implanted stimulation systems; other methods of walking, except the common one or the static position; stimulation with using the training devices (exercise bicycle and others); research works employing the survey method; the ones where stimulation was used as the experimental variable; the research works with multi-channel constant stimulation; multi-channel stimulation in healthy test subjects.

NUMBER OF CHANNELS AND THE MUSCLES STIMULATED

FES was first used for compensating the foot drop syndrome in rehabilitation after a cerebrovascular stroke by V.T. Liberson et al. [13] in 1961. The authors have obtained positive results of correcting the foot drop symptom in patients after the CVA. Later on, multiple research works have demonstrated that FES is an effective method of improving the motor function [14], of increasing the walking speed [15] and of decreasing the degree of intensity for spasticity after a cerebrovascular stroke. With this, it is known that single- or double-channel FES in a sufficiently effective way stimulates the dorsal flexing of the ankle joint, which is accompanied by the decreased flexing amplitude in the knee joint along with the plantar flexion of the ankle joint at the second half of the stance phase, at the beginning of the swing phase [11], decreasing the repulsive momentum generated at the end of the stance phase. The application of multi-channel FES can compensate and provide the insufficient momentum force. In particular, a number of research works reported the positive results of using MFES in early rehabilitation of individuals after the CVA in a context of affecting the balance control and mobility. In the research works by the groups headed by Z. Tan [16] and T. Yan [17], it was demonstrated that using the four-channel FES for the main flexors-extensor muscles of thigh and shin can improve the motor function, the balance, the ability to walk, as well as the ability to perform everyday activities in CVA patients at the early rehabilitation period.

In the research on the effects of FES of the anterior tibial muscle, an effect of increasing the walking speed and frequency was described [14], with this, the FES of the anterior tibial muscle, of the long peroneal muscle, of the quadriceps and the *hamstring* muscles, was to a significant extent increasing the efficiency and the speed of walking [18], while the involvement of the femoral abductor stimulation into the process has stabilized the positioning of the coxofemoral joint itself and to a significant extent has increased the ability of unassisted walking, contributing to re-gaining the balance [19].

[1] Decree issued by the Ministry of Health of Russia dated July 31, 2020, No. 788n «Concerning the approval of the Procedure of organizing the medical rehabilitation of adults». Access mode: https://www.garant.ru/products/ipo/prime/doc/74581688/?sclid=mc8qui3cc6321811374

Upon taking off the table the separate topic of stimulation in cases of foot drop syndrome, in other cases the muscles used for FES are the main flexors-extensors of the shin and the thigh. When training the walking motions using FES, the main target muscles are the groups represented in table 1 [17, 20–25].

OPTIMAL TIMING PARAMETERS OF FUNCTIONAL ELECTROSTIMULATION

The main MFES parameters may include the following: the duration of a single procedure, the number of procedures per weeks and the total course duration. The conducted research works describe various timing parameters of the procedure. For example, the possibility of using the stimulation lasting from 15–30 minutes [26] to 30–45 minutes [17, 27] was studied. In general, it is worth noting that the optimal timing of FES, for example, in case of correcting the foot drop symptom in CVA patients, can vary extensively. In particular, S.K. Sabut et al. [15] report the positive results of daily usage of the device with sessions lasting 20–30 minutes. Some research works describe the gradual increase of session duration (from 15 minutes during the first week to 30–45 minutes in the following weeks [14]), which can contribute to better adaptation of patients to electric stimulation and can decrease the risk of muscular fatigue at the initial stages of rehabilitation, at the same time, the stimulation device itself is claimed to be the means of prosthetic replacement for the function.

Regarding the frequency of training, the majority of FES protocols recommend arranging the sessions not less than 5 times a week [17, 28], though no justification is provided by the authors. In the research by Z. Hong et al. [29] with arranging the FES training sessions among the patients at the chronic stage of stroke, the sessions lasted 20 minutes 3 times a week for 7 weeks with good clinical effect. In the systematic review published in 2024 [30], the authors came to the conclusion that less long training sessions are more effective than the long-lasting ones.

Thus, the practice of using FES most frequently includes the so-called standard protocols, which are used regardless of the stroke period, namely: from 3 to 5 training sessions a week with the duration from 30 to 60 minutes depending on the patient status with a total course of 3–12 weeks for the purpose of improving the walking parameters, such as speed and balance, as well as for the correction of spasticity [14, 31]. If necessary, the FES duration can reach up to 6 months for achieving the stable effect with sessions performed daily or several times a week [25]. It was noted that the early initiation of FES and its long-term application are of fundamental importance for achieving the optimal results.

Currently, a trend can be seen towards combining the MFES itself with other technologies of training to walk (treadmill sessions, motorized exercise bicycle training sessions etc.) for increasing the functionality of the process [32, 33].

MODES OF FUNCTIONAL ELECTROSTIMULATION

Currently, the stimulation models known as the variable-frequency trains (VFT), have a number of benefits comparing to the traditional constant-frequency trains (CFT). In particular, it was noted that the VFT enhance the isometric [34] and non-isometric [35] parameters of the muscles, as

Table 1

Muscles of the lower limb and their combinations used for functional electrostimulation

Source	Stimulated muscles
Allen, 2018 [20]; Aout, 2023 [21]	The anterior tibial muscle has the fundamental importance for performing the dorsal flexion of the ankle joint at the swing phase
Allen, 2018 [20]; Aout, 2023 [21]	Plantar flexors of the ankle joint are stimulated at the second half of the stance phase to improve the repulsion and frontal motion when walking
Hakansson, 2011 [22]	Isolated stimulation of only the anterior tibial and gastrocnemial muscle
Tenniglo, 2018 [23]	Stimulation of only the posterior group of thigh muscles
Purohit, 2024 [24]	The quadriceps muscle is being selectively stimulated for the purpose of improving the stability of the lower limb
Shin, 2022 [25]	The abductor muscle of the thigh and the gluteus maximus muscle for supporting the vertical position of the body when walking
Yan, 2005 [17]	Four muscles simultaneously (main flexors-extensors) — anterior tibial, medial gastrocnemial, whole posterior group of thigh muscles and the quadriceps muscle of thigh

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shown in the healthy quadriceps muscles of the thigh comparing to the CFT of similar frequency, especially when the muscles are tired. Besides providing the improved performance of skeletal muscles, the VFT are considered a more physiologically justified stimulation pattern comparing to the CFT [36].

The difficulties of predicting the effect of FES have multiple factors, which are difficult to take into account in the real-life settings: thus, for example, the mode of muscles working can significantly change at various motion phases, the response to FES can also be different. For more precise exposure, mathematical models are being developed that operate the data sets accessible as of today [12], nevertheless, the information currently available is insufficient and the research must be continued.

The main FES parameters in the published articles were summarized in table 2 [10, 11, 14–18, 20, 22–24, 26–28, 31–33, 37–41]. The analysis of stimulation parameters has revealed a wide variability of FES protocols used by various investigators for various forms and clinical stages of stroke. The stimulation frequency varies from 30 to 100 Hz with the predominance of the 30–40 Hz range in the majority of research works. It is important to note that only 8 of 22 research works state the current force. The average procedure duration is approximately 30 minutes with the marginal values from 15 to 60 minutes. Notably, the multiplicity of the procedures varies from 2 to 7 a week (with a mean of 5 sessions) and the total course duration — from 3 to 30 weeks, more often 4–6 weeks.

The synchronization of FES with the walking cycle represents a critically important aspect of the effective usage of the methods. The analysis of literature data shows a variety of synchronization methods applied in various researches. Thus, the most widespread is the usage of contact switches located in the shoes of the patient [14, 18, 21, 22, 37]. Contact sensors determine the step cycle, then the algorithm supposes the presence of the needed delay before switching on one or another channel, however, contact sensors are temperamental, they have a certain activation threshold, bouncing and other technical drawbacks. More modern systems use the data from the accelerometers [27, 38] or more complex inertial systems [11], which allows for increasing the accuracy of determining the step cycle. Some research works employ the synchronization based on the EMG-activity of the contralateral limb [16] or of the paretic limb itself [32], as well as manual activation [10, 17]. Modern developments include the integration of inertial sensors (inertial measurement unit, IMU) with the algorithms of machine learning [39], which potentially can provide a more adaptive and personalized synchronization of stimulation with the individual features of the pathological gait in a patient.

EXTERNAL ACCESSORIES FOR THE MOTION ORGANIZATION

The complete correction of known disorders when walking using FES is not possible for the majority of patients, which is why, during the course of stimulation, as well as in everyday life, the patients continue to receive aid with special technical means that not just assist the movement, but also organize it. Such technical means include both the simple ortheses for supporting the normal positioning of the ankle joint [40] and much more sophisticated training equipment along with walking imitators, the robotic devices and neuroprostheses [41]. As of today, the hybrid set including the exoskeleton combined with FES is estimated as one of the most promising technologies for restoring the walking function. In a number of research works, it was noted that using FES causes the rapid onset of muscular fatigue [42], which, in turn, decreases the ability of the muscles to maintain or produce the contraction force and significantly decreases the training session time. Based on this, attempts were made to combine FES with passive orthesis [43], which was used to dampen the consequences of muscular fatigue, but these devices failed to provide an additional torsional moment required, in particular, for the knee joints. Autonomous exoskeletons [44, 45] can compensate this and other moments: in this combination, the supportive robotic aid decreases the general operating cycle of muscle contractions induced by FES, also delaying the onset of muscular fatigue during the course of physical exercises with high torsional moment, such as the “sit-stand”. Besides, active muscle contractions induced by FES, promote to the neuroplasticity that restore the lost functioning of the limb, unlike the electrically driven exoskeletons, which provide only passive motions [46].

Exoskeletons with integrated FES have appeared on the Russian medical market at the beginning of 2020s. The topic of integration was discussed previously [47], which lead to the increase in the number of such devices offered at the national medical market and allowed for arranging a research on the combination of FES when moving with the aid of the exoskeleton among the patients after a cerebral stroke [48, 49]. The authors have revealed a positive effect for the immediate and early rehabilitation periods, however, so far the experience of using such devices is significantly limited.

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Table 2

Stimulation parameters

Frequency	Frequency, Hz	Single impulse duration	Session duration, min	Current, mA	Number of sessions per week	Course duration, weeks	Synchronization method
Hakansson, 2011 [22]	30	300 msec	30	-	3	12	Contact switches
Tenniglo, 2018 [23]	40	125–475	-	-	3	5	Contact switches
Nam, 2019 [37]	80	300	15	-	5	4	Contact switches
Kojović, 2009 [27]	50	400 μsec	45	12–38	5	4	Accelerometer/ contact switches
Kesar, 2010 [11]	30	300 μsec	20–30	Not provided	3–5	4	Gyroscope / Goniometer Contact switches
Yang, 2009 [18]	40	250 μsec	20	Not provided	5	4	Contact switches
Sabut, 2010 [14]	40	300 μsec	First week: 15 Following weeks: 30–45	20–60	5	12	Contact switches
Sabut, 2011 [15]	35	280 μsec	60	-	5	12	Contact switches
Tan, 2014 [16]	30	200 μsec	30	Not provided	5	3	EMG in the contralateral limb
Yan, 2005 [17]	30	300 μsec	60	20–30	5	3	Manual trigger at the swing phase
Bloemendaal, 2016 [26]	35	350 μsec	30	10–50	5	4	Contact switches (force)
Lee, 2013 [32]	Not provided	50 μsec	30	Not provided	5	4	EMG-activity
Alon, 2011 [33]	50	250 μsec	30	Not provided	3	8	Synchrodrive
Sharif, 2017 [31]	40	Not provided	20–30	Not provided	5	6	-
Dantas, 2023 [38]	-	-	30	-	2	6	Accelerometer
Purohit, 2024 [24]	20–45	450 msec	45	30–55	-	-	-
Allen, 2018 [20]	Not provided	Not provided	30	Not provided	3	6	Contact switches
Ji, 2022 [39]	30–45	200–350 μsec	25	25–70	4	5	Inertial + machine learning
Moe, 1962 [10]	30	0.1–0.5 msec	15	Not provided	5	6	Manual trigger at the swing phase
Cheng, 2010 [28]	40	200–300 μsec	30	Not provided	3	4	-
Kluding, 2013 [40]	30–50	200 μsec	30	Not provided	2	30	Contact switches
Thrasher, 2006 [41]	35	300 μsec	15–30	18–110	2–5	12–18	Manual trigger at the swing phase
Bao, 2020 [42]	30	0.3	45	15	5	8	Contact switches

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Due to the fact that the main function of the exoskeleton is the decrease of the excessive monotonous loading and easing the hard work of the nursing medical staff [50], the usage of additional methods of increasing the training efficiency is deemed justified. In a later research work by M.T. Dantas et al. [38], it was noted that FES, undoubtedly, positively contributes to the training among the post-stroke patients using the exoskeleton and proposes an adaptive stimulation algorithm with taking into consideration the motion amplitude developed.

THE STAGING OF TEACHING THE MOTOR SKILLS

The process of teaching the motor skills can and must be analyzed stagewise [51]. Even though, in practice, the transition from one stage of learning the motor skills to another is smooth and it is not always clearly understandable at which specific stage the patient is currently, three phases can be isolated — the initial, the associative and the autonomous.

At the initial stage of learning the motor skills, or at the so-called cognitive stage, in order to master a specific motor task, various strategies are employed for selecting the optimal motion variant. The support from the rehabilitation therapist at this stage is extremely important and, depending on the degree of deficit in a patient, it can be implemented either in the form of physical or the verbal feedback [52].

When transitioning to the associative stage of learning, the patient demonstrates a sharper skill of the motion trained. The motor training task is done with lesser variability, until the optimal strategy could be finally found [53]. From this moment, the specialist shall restrain from manual support, but the target feedback is still important. This feedback should be provided with a delay relative to the motor task to avoid overlapping with the inner feedback for the motion control [54]. After the motion strategy is defined, the training sessions can be modified a little.

The autonomous stage suggests mainly the automatic motor skill, the task should be repeatedly modified until the moment of the patient being capable of doing it in any type of environment conditions. At the autonomous stage of motor learning, the program is already automated: this means that the motion can be done in the almost optimal manner, not requiring significant attention or concentration [53]. At this stage, it is possible to more precisely focus on the separate components of motion to preserve them. Variations of exercises, as well as the inclusion of higher difficulty elements, are now necessary for supporting the motivation of the patient [52].

THE EFFICIENCY OF FUNCTIONAL ELECTROSTIMULATION AND THE TECHNICAL ASPECTS

In a randomized research by Z. Tan et al. [16], the efficient rehabilitation cycle lasted for 3 weeks, while the improvements could persist within at least 3 months upon the end of the course. Special attention is attracted by the time of the onset of the possible positive FES effect, for example, the increase of the walking speed. It was noted that the gradual increase of this parameter occurs when using FES within the first 18 weeks, but later on no changes could be observed [40].

In the accessible literature, researchers do not emphasize in any manner the clinical form of stroke and which time period exactly after the CVA is the best to initiate training. In a research by T.M. Kesar et al. [11], it was reported that FES is used to restore the lost or abnormal motions. Nevertheless, the most effective FES is considered the one that was initiated at the subacute stage of stroke, usually within several weeks or months after a cerebrovascular accident, for this period has the fundamental importance for the maximal restoration of motor activity and for functional improvement [31]. Arranging the FES in 6 months from the moment of disease onset is also considered as effective, for the sessions allow for preserving or improving the walking function and mobility, though the speed of developing the functional changes is already not so high [21]. According to the data from the review by Z. Hong et al. [29], FES also remains effective in patients at the chronic stage of stroke. It was shown that the quality of walking could be improved along with its symmetry when using the stimulation of the anterior tibial muscle and of the triceps muscle of the calf in patients with insufficient motion control in the ankle joint. In one of the recent systematic reviews, the authors make a cautious conclusion that FES can be more effective for patients exactly at the chronic phase [30]. Similar conclusion was drawn up in the research by M.J. Nam et al. [37]: based on the proprietary data, the authors recommend FES for patients at the chronic stage of stroke.

Among the technical aspects of arranging the FES, the importance of correct positioning of electrodes at the stimulated muscles was noted: in order to fulfill this task, it is necessary not only to have the knowledge of functional anatomy, but also the possibility of individual approach in each specific case. At the present moment, there is a general rule for the positioning of electrodes: the electrodes are first placed above the nerve(s) innervating the stimulated muscle, after which stimulation is undertaken. If the resulting motion is desirable, the positioning remains. In case of the

negative result, the electrodes should be repositioned (usually by not more than several centimeters) and the test should be repeated until achieving the desired motion, with this, the patient should have the motivation for conducting the FES [55]. The majority of manufacturers of such an equipment provide the stereotypical schemes of electrode positioning without taking into account the places were the nerves originate, but recommending that the main belly of the muscle is positioned between the electrodes. In this case, the property used for the applied stimulation is the direct excitation of muscle fibers.

DISCUSSION

The majority of research works on FES is still focused on the single-channel stimulation for compensating the foot drop syndrome [20–22], with this, the multi-channel stimulation in various forms is recognized as more effective, however, it is much less frequently applied. There are various variants of it, but the main ones include four groups of flexors-extensors of the lower limb: the quadriceps muscle of thigh (or its separate head), the posterior group of thigh muscles (or separate muscles), the anterior tibial muscle and one or both gastrocnemial muscles. Our analysis has shown that the clinical reports on using the MFES in patients after an episode of cerebral stroke were quite few. There are only single ones that are modern. With this, there are publications submitted over the last years which are of technical or experimental nature and fall outside the ranges of the inclusion criteria for this review.

The duration of the FES session significantly varies (from 15 to 60 minutes), with the absence of justification for this or that duration provided by the authors. In fact, the spread of the parameter values, where the minimal value is 4 times less than the maximal one, speaks for itself. The FES parameters were also not matching the physical stamina of the patients. It is evident that this or that duration should be manageable for the whole test group, but this is all that could be suggested taking into consideration that the patients with similar clinical form and the degree of hemiparesis can show various exercise tolerance and, probably, require different timings of FES sessions. Our suggestion is that the specialists involved into performing the FES sessions commonly remain within the frames of treatment schemes approved, in which the session time is some kind of a constant not anticipating any individual approach.

The number of procedures per week is also subject to variability, mainly within the range from 3 to 5. This aspect is also presented as a constant with no discussion, why this or that number is used. Evidently, it is related to the organizational aspects of the rehabilitation process, not to the physiological justification. The trend of arranging 5 sessions a week, as it is set in the research works by J.S. Cheng [28] and T. Yan [17], can be resulting from the reference to the number of work days and not the optimal stimulation mode. For the first case (3 days a week) they come every other day (Monday, Wednesday, Friday), while for the second one (5 days a week) — all the work days. Thus, even this parameter is not in fact related to the clinical form or to the status of the patient.

The duration of FES course varies with a factor of eight — from 3 to 24 weeks, with this, the number of authors report that the longer the course is, the higher is its efficiency [23]. The objective criteria for the duration of a certain course were also not provided by the authors. It can be agreed that the changes in the walking function as a result of cerebral stroke by no means can be restored in all the cases. The remaining stable abnormalities require supporting activities for the life term, and in this context, the long-term courses can be surely justified. But it seems that the judicious balance here will depend on very numerous factors, including the system of organizing the rehabilitation therapy, and it is still not the object of research.

As for the modes of used FES, the majority of research works use constant frequency. This aspect is also not supported by any explanations: the authors just state the name of the equipment used. And here, the most important role is played by two circumstances. The first one that the stimulation devices with constant frequency are technically much simpler and more available for use [56]. These reasons are already enough to have the overwhelming dominance in the research works. Second off — the methods with variable frequency are not just incomparably more complex: the experience of their application is very limited, while the criteria for controlling the new variable (the frequency) are even less clear, with the effect of decreased spasticity — the one of the essential ones — is reported for the stimulation with constant frequency current [57]. Besides, it is known that various muscles, even at the normal conditions, have various sensitivity and response to changing the frequency at various activity phases [58], and we have even less understanding of the various conditions of muscles in patients after a cerebral stroke, depending on its specific form. Besides, it is necessary to note that applying the data for healthy muscles to the muscles with pathological neuromuscular regulation is still not possible. Another essential moment is that the

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pathological locomotion itself results in changes in the functions of the muscles [56], due to which, the cause and effect can not always be clearly differentiated.

The analysis of published research data demonstrates significant variability in the parameters of electric stimulation. The stimulation frequency in the majority of research works varies from 30 to 50 Hz [16, 17, 22, 27], though separate articles describe both the lower (20–45 Hz [24]) and significantly higher (80 Hz [37]) frequencies. The 30–50 Hz frequency has a certain physiological justification [58], however, for patients after a cerebrovascular stroke presenting with hemiparesis, the status of the muscles changes from the immediate to the residual period. What frequency for which type of muscle impairment and at what phase would be the best, remains disputable.

The duration of impulses also significantly differs — from 50 μsec [32] to 450 μsec [24], with the most commonly used range being the 200–350 μsec. The impulse duration has a number of justified criteria [58], but what needs to be taken as guidance when determining this parameter for each specific muscle in the given patient remains unclear. With other factors being equal, the longer impulse carries more energy, but this is probably and so far the only evident criterion to be used to achieve the required response from the muscle.

The current amplitude, where provided, usually varies from 10–12 to 60–70 mA with an individual adjustment for each patient. Oftentimes, the amplitude is not reported in the research at all, and this is not a mistake made by the authors. The thing is that this parameter is too much related to many other factors, among which are the following: the surface area of the electrodes employed, the stimulated muscle itself and its status, the thickness of subcutaneous-fatty tissue, some technical features of the stimulating channel etc. Thus, even when the current amplitude is mentioned, this can only serve as the guiding point.

It is important to note the absence of unified criteria for choosing the stimulation parameters for specific groups of patients. The majority of protocols are developed empirically, without the clear justification of selecting these or those parameters. S. Chen et al. [30] in their research note the urgent need for studying the specific features of operating with FES with various adjustments of stimulation frequency and other parameters.

The topic of synchronizing FES with walking is technically the most complex. The method of contact switches, which is used in the majority of cases, is the result of permissible simplification. The contact sensors themselves are used for various types and constructions, but they operate in harsh conditions of the body weight affecting them and, with this, they need to have a low activation threshold and a short (within milliseconds) hysteresis (returning to initial conditions upon the removal of the load). These issues fall outside the frames of solely medical field, however, in the current century, new methods were proposed for detecting the step cycle phase, in particular, the inertial sensors, which at the present moment have almost completely replaced the contact sensors in the autonomous systems for the correction of foot drop. Synchrodrives can be used only as a part of robotic devices with walking imitation, which limits their usage. The methods for initiating a pack of stimulating impulses based on the EMG-activity detection is another new method. From the methodical point of view, it can be deemed adequate only for the muscles which have no phasic activity impairments. In other cases, this method is inapplicable. How precisely the EMG-signal can detect the time parameters of synchronization, also remains disputable. In one of the research works [16] this method was used in the modification that employed the unaffected side for initiating the FES on the paretic one. Such a variant can not be considered as good or applicable for the reason that the EMG-activity on the unaffected side is not compensatory modified, but also the step cycles themselves have substantial reciprocal shifts [7] i.e. the shifting of step cycles relative to each other is present, which may reach the values of 10–30% of the step cycle. Thus, the error of “detecting” the step cycle becomes unacceptable. Nevertheless, the synchronization based on the EMG-activity can be a very reasonable choice for voluntary movements, but it is already out of the frames of the walking function. The manual option of activating FES might as well have only the historical value due to its extreme inaccuracy.

There is no doubt that, in cases of significantly impaired walking biomechanics, its feasible correction may be required. The matter if it is possible to achieve the decrease in the degree of motor disorders by this, remains unexplored and requires further research activities. At what degree and for which clinical cases the exoskeleton or other devices with integrated stimulation system could be useful, the results of further research works will show.

The staging of rehabilitation can serve the purpose of the individual estimation of the current status of the patient and its dynamic changes, with this in mind and with all the other factors being equal, it gives ground for using the MFES method from the first days of starting to teach the patient to move without assistance.

It could be stated that there is no existing all-purpose MFES protocol fitting all the patients with a history of cerebrovascular stroke. The differentiated approach is necessary, the one taking into account several key factors, the most important of which are the following.

Type of motor disorder. For the patients with predominant decrease of muscle strength without pronounced spasticity, the effective stimulation could be the one having the parameters aimed at strengthening the muscles and at improving their stamina (low frequency — 20–30 Hz, longer sessions). In patients with significant spasticity, the more effective could be the mode with high stimulation frequency (more than 50 Hz) [15, 57].

Rehabilitation period after a cerebrovascular stroke. At the immediate and the early period of rehabilitation, MFES can contribute to the prevention of developing pathological motor stereotypes and could be a valuable addition to the traditional methods of rehabilitation. At the residual stage, MFES can be especially useful for overcoming the rehabilitation plateau and for improving the functional capabilities [30].

Cognitive abilities of the patient. For patients with cognitive disorders, the more preferable could be the systems with automatic synchronization, not requiring the active participation of the patient in the stimulation process. For patients with intact cognitive functions, the more effective systems could be the ones with biological feedback, requiring the active participation of the patient [52].

CONCLUSION

Multi-channel functional electrostimulation is considered an effective method of restoring the walking function in patients after a cerebrovascular stroke, however, the existing application protocols are characterized by the significant variability of parameters without the clear physiological justification. It was found that the recommended duration of procedures varies from 15 to 60 minutes, the stimulation frequency — from 20 to 80 Hz, while the course duration — from 3 to 24 weeks, with the choice of specific parameters having a predominantly empirical pattern and depending on the organizational factors, not on the clinical status of the patient. A necessity was demonstrated for developing a differentiated approach to the application of MFES with taking into consideration the type of motor disorder, the period of rehabilitation after a cerebrovascular stroke and the cognitive capabilities of the patient. The optimal technical parameters of stimulation were defined: 30–50 Hz frequency, 200–300 μsec impulse duration with individual adjustment of amplitude and obligatory synchronization with the step cycle in the paretic limb. Modern trends of improving the method include the integration of MFES and of the robotic devices and systems with biological feedback, which opens new possibilities for personalized rehabilitation. The obtained results justify the necessity of arranging large-scale clinical research for the standardization of MFES protocols and for compiling the scientifically justified recommendations on its use in various clinical situations.

ADDITIONAL INFORMATION

Author contributions. *D.V. Skvortsov:* research concept development, literature search and analysis, writing the original draft; *L.V. Klimov:* literature search, data analysis, editing, and results interpretation; *D.A. Lobunko:* literature search, text editing, and data visualization; *G.E. Ivanova:* project supervision and organizational support. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Suprascapular Neuropathy Combined with Massive Rotator Cuff Tears: Clinical Signs, Diagnostics, Treatment

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ABSTRACT

Suprascapular neuropathy is a type of disease, which up until recently was considered quite rare and observed mainly among the athletes. On the contrary, this problem is observed quite often, especially as a professional disease among the individuals involved in heavy manual labour. The syndrome of suprascapular nerve compression is a complex problem, combining a multitude of reasons and resulting in the atrophy of the supraspinal and infraspinous muscles. The compression of the suprascapular nerve is developing due to its complex anatomy, the presence of additional bony and other types of structures in the area of the scapular notch, as well as due to the traumatic lesions of the rotator cuff and of the scapular spine. There is an opinion that the contraction of the damaged supraspinal and infraspinous muscles may cause contusion- related changes in the suprascapular nerve, which may persist after the reconstruction of the rotator cuff. The provided research summarizes the data available on the suprascapular neuropathy, especially combined with massive rotator cuff tears, as well as on the reasons of its development, the clinical manifestations, the diagnostics and the comparative results for various treatment methods. An analysis was conducted of the main research results obtained using the surgical treatment for suprascapular neuropathy, in particular, the arthroscopic decompression combined with the treatment of rotator cuff abnormalities. The analysis of literature data has shown that, in case of the presence of space-occupying masses or bone deformities in the area of the scapular notch, surgical correction shows significant positive results. In case of damaged rotator cuff, the combination of arthroscopic release of the suprascapular nerve with its reconstruction provides good clinical results, promoting to the decrease of the pain syndrome during the postoperative period, however, no significant differences were reported when restoring the rotator cuff both with the release procedure and without it. Most part of the patients with chronic pain syndrome and degenerative changes can be successfully treated conservatively. Despite the fact that the relation of rotator cuff tears and suprascapular neuropathy is undoubtful, many researchers describe the absence of statistically significant difference in the clinical results of reconstructing the rotator cuff together with arranging the procedure of arthroscopic release and without it. Thus, probably, the indications to arthroscopic release of the suprascapular nerve should be clearly limited to cases of its neuropathy based on the data obtained during the research including larger samples of patients.

Keywords: *suprascapular neuropathy; rotator cuff; suprascapular nerve; arthroscopic decompression of the suprascapular nerve.*

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INTRODUCTION

Pain in the shoulder joint is a quite widespread orthopedic problem. Shoulder pain is the third most widespread complaint related to the musculoskeletal system in the primary medical aid [1, 2]. Complaints of pain related directly to the shoulder joint most frequently are a consequence of damaging the bone and cartilage structures of the shoulder, the acromioclavicular or sternoclavicular joints, as well as of the rotator cuff or other soft tissues of the shoulder complex. The incidence of shoulder pain in the society varies widely and, according to the data from latest research works, it equals 16% (ranging from 0.67 to 55.2%). The parameters are higher for women comparing to men. The incidence of shoulder pain varies from 7.7 to 62 per 1000 persons a year (with the mean values of 37.8 per 1000 persons a year) [3]. Notably, 20–40% of the patients show asymptomatic ruptures of the rotator cuff, indicating that the structural abnormality may not always manifest clinically, also impairing the function of the shoulder

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Нейропатия надлопаточного нерва в сочетании с массивными разрывами вращательной манжеты плеча: клиническая картина, диагностика, лечение

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АННОТАЦИЯ

Нейропатия надлопаточного нерва — вид патологии, который до недавнего времени считался довольно редким и наблюдался в основном у спортсменов. На самом деле данная проблема встречается достаточно часто, особенно в качестве профессионального заболевания у людей, занимающихся тяжёлым физическим трудом. Синдром сдавления надлопаточного нерва — проблема комплексная, сочетающая множество причин, приводящая к атрофии надостной и подостной мышц. Компрессия надлопаточного нерва обусловлена его сложной анатомией, наличием дополнительных костных и других образований в области вырезки лопатки, а также травматическими повреждениями вращательной манжеты плеча и ости лопатки. Существует мнение, что сокращение повреждённых надостной и подостной мышц могут вызывать контузионные изменения надлопаточного нерва, которые могут сохраняться после реконструкции вращательной манжеты плеча. В представленной работе обобщены имеющиеся данные о нейропатии надлопаточного нерва, особенно в сочетании с массивными разрывами вращательной манжеты плеча, а также о причинах возникновения, клинических проявлениях, диагностике, сравнительных результатах различных методов лечения. Проведён анализ основных результатов хирургического лечения нейропатии надлопаточного нерва, в частности артроскопической декомпрессии в сочетании с лечением патологии вращательной манжеты плеча. Анализ литературы показал, что при наличии объёмных образований, костных деформаций в области вырезки лопатки хирургическая коррекция имеет значимые положительные результаты. В случае повреждения вращательной манжеты плеча сочетание артроскопического релиза надлопаточного нерва с её реконструкцией даёт хорошие клинические результаты, способствует уменьшению болевого синдрома в послеоперационном периоде, однако значимых различий при восстановлении вращательной манжеты как с процедурой релиза, так и без неё не выявлено. Бóльшая часть пациентов с хроническим болевым синдромом и дегенеративными изменениями могут успешно лечиться консервативно. Несмотря на то, что связь разрывов вращательной манжеты плеча и нейропатии надлопаточного нерва не вызывает сомнений, многие исследователи описывают отсутствие статистически значимой разницы в клинических результатах реконструкции вращательной манжеты плеча с проведением процедуры артроскопического релиза и без таковой. Таким образом, вероятно, следует более чётко ограничить показания к артроскопическому релизу надлопаточного нерва при его нейропатии на основании данных исследования на бóльших выборках пациентов.

Ключевые слова: *нейропатия надлопаточного нерва; вращательная манжета; надлопаточный нерв; артроскопическая декомпрессия надлопаточного нерва.*

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joint [4]. The disease of the suprascapular nerve recently has become one of the widespread reasons of pain and weakness in the shoulder joint [4, 5].

Recently, a multitude of scientific articles were published on the incidence, the causes, the risk factors and the possible variants of conservative and surgical treatment for suprascapular neuropathy combined with massive ruptures of the rotator cuff, however, no unified opinion on the treatment tactics was compiled based on the literature data.

In the provided review, we have summarized the data available as of today on suprascapular neuropathy, especially when combined with massive rotator cuff tears, as well as on the reasons of its development, on the clinical manifestations, on the diagnostics and on the comparative results of various treatment methods.

Methodology of searching the sources

The present review included the publications from the Pubmed database submitted before the year of 2024 (inclusive). The search was carried out using the following key words: “suprascapular nerve”, “suprascapular neuropathy”, “suprascapular notch”, “spinoglenoid notch”, “arthroscopic decompression (release) of the suprascapular nerve”, “massive tears of the rotator cuff”. An analysis was conducted on the main clinical results of surgical treatment.

SUPRASCAPULAR NEUROPATHY COMBINED WITH MASSIVE ROTATOR CUFF TEAR: REASONS OF DEVELOPMENT, RISK FACTORS, TREATMENT VARIANTS

Anatomic features

The suprascapular nerve compression syndrome is to a great extent caused by the complex anatomical structure of the nerve itself, which is formed by the branches of the upper trunk of the brachial plexus [6–8], innervating the supraspinal and the infraspinous muscles, the acromioclavicular joint, the skin of the posterior surface of the shoulder. Within the structure of the suprascapular nerve, there are two possible areas of entrapment — the area of the suprascapular notch (Fig. 1) and the area of the spinoglenoid notch [9]. The variant of the anatomical structure of the suprascapular notch can be the reason of possible compression of the suprascapular nerve. There are six types of the suprascapular notch structure: type 1 — recess; type 2 — shallow V-shaped notch; type 3 — U-shaped notch; type 4 — deep V-shaped notch; type 5 — U-shaped notch with partial ossification of the ligament; type 6 — complete ossification of the transverse ligament [10]. Specifically this anatomical variant determines the complexity of diagnostics of suprascapular neuropathy, which more often develops in cases of type 5 and type 6 scapular anatomy variants.

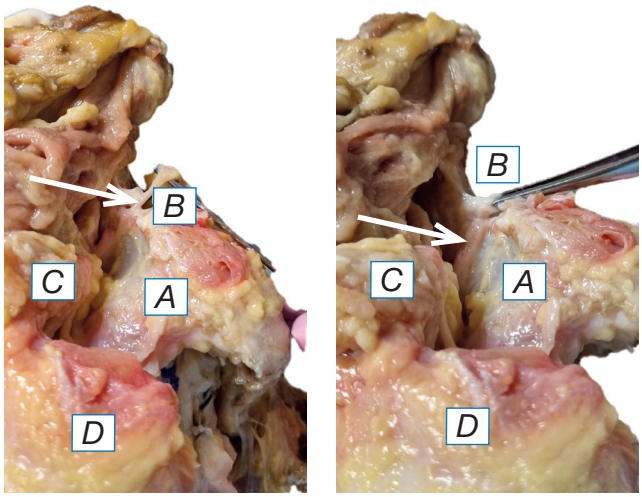

Fig. 1. The area of the suprascapular ligament. The scapula (*A*), the transverse ligament of the scapula (*B*), which is dissected on the left and intact on the right, the diverted supraspinatus muscle (*C*), the acromion (*D*). The arrow indicates the suprascapular nerve.

Pathophysiology and reasons of developing the suprascapular neuropathy

The impaired functions of the shoulder joint can be resulting both from the damage of the rotator cuff and from the impairment of its innervation. Two possible levels are described for damaging the suprascapular nerve — the proximal one (between the scalene muscles and the Erb’s point, i.e. the place of origination of the brachial plexus) and the distal one (between the suprascapular notch along the upper margin of the scapula and the infraspinous muscle). When moving the shoulder forward during the external rotation, the fibers of the suprascapular nerve become dislocated along with the stretching of the nerve: the area of its cross-section decreases, while pressure inside the nerve bundles builds up [5, 11]. If, upon the stretching of the nerve, its limit of elasticity does not get exceeded, the nerve restores its initial length, but if its extension limit gets exceeded, the nerve deforms, not being capable of restoring its original length. Thus, repeated rotation motions in the shoulder are the reason of repeated injury or compression of the suprascapular nerve [5]. Nerve compression can also develop in case of bone tissue traumatic changes and in case of additional bone tissue formation in the scapula, in case of space-occupying cysts or tumors in the area of the scapular notch [12–14].

Currently, a strong interest is noted in terms of the relation between the suprascapular neuropathy and the massive retraction of the fibers in cases of rotator cuff tears. M.J. Albritton et al. [15] in their research have focused the attention on the fact that medial retraction of the supraspinal muscle tendon drastically increases the tension in the nerve. It was found that there is a tension limit in cases of lateralization of the supraspinal and infraspinous muscles when conducting the surgical treatment of the rotator cuff suture, for this may lead to excessive tension in the branches of the suprascapular nerve. In turn, there is an opinion that, in patients with increased range of motion in the shoulder joint and with isolated injuries of the subscapular muscle, there is a risk of developing suprascapular neuropathy [16].

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Clinical manifestations

The clinical manifestations of neuropathy mainly depend on the location of the lesion and on the reasons of compression [9, 13]. Upon the detailed survey and assessment of the patient, it is possible to find the presence of impaired dermal sensitivity in the area of the posterior segments of the shoulder, as well as the location of pain in the scapular area, which can increase upon the adduction of the humeral bone with it simultaneous inward rotation, or when flexing the shoulder joint with simultaneous adduction of the shoulder, also when turning the head to the opposite side [17]. On palpation, the area of the supraspinal fossa can be sharply painful, other findings may include positive hyperextension tests [18] and the tests of arm adduction in the transverse direction (the test described by Planche: the patient is asked to move the hand backwards and to turn it inwards, if the patient has complaints of increased pain in the posterior part of the shoulder, the test is considered positive) [19]. Upon visual examination, attention should be paid to the contralateral side: in cases of suprascapular neuropathy, the findings include a pronounced hypotrophy in the supraspinal and infraspinous muscles. The compression of the nerve in the suprascapular notch may lead to the loss of more than 75% of strength of abduction and external rotation [20]. In case of nerve injury in the area of the spinoglenoid notch, there are no sensitivity disorders or pain syndrome observed, only isolated hypotrophy of the subscapular muscle and weakness of external rotation can be noted [21].

The differential diagnostics of this disease should include the radiculopathies at the C5 level in the cervical spine, the disease of the brachial plexus, the spinal muscular amyotrophies, as well as other various secondary neuropathies [19].

Diagnostic methods of examination

When suspecting the abnormalities in the rotator cuff, including the combination with suprascapular neuropathy, for the purpose of ruling out the bone tissue lesions, standard radiology should be carried out using frontal projection, this procedure should be supplemented with the image of the Stryker suprascapular notch view — an image obtained using special positioning (the patient should be positioned supine, placing the palm of the impaired limb on the forehead, while the X-ray beam should be directed at a 15° angle to the head) for the evaluation of the suprascapular notch and of the spinoglenoid notch (Stryker's method) [12].

For the purpose of ruling out the bone tissue lesions in the scapula, it is also possible to use computed tomography, including the one with 3D-reconstruction, which can show the presence of specific anatomical structures damaging the nerve [22]. Thus, K. Honoki et al. [22] have found that the ossification of the transverse ligament in the scapula was significantly more commonly found in elderly patients, which rather indicates the age-related changes. Besides, there was no direct correlation found between the narrow scapular notch, the ossification of the abovementioned ligament and the development of suprascapular neuropathy.

The gold standard of examination is the magnetic resonance imaging (MRI) as the most accurate method of detecting abnormalities in the soft tissues of the shoulder joint. MRI allows for evaluating the changes (the damage) in the rotator cuff muscles, the degree of dislocation (retraction) of tendons, for detecting the fatty degeneration/hypotrophy/atrophy in the supraspinal and infraspinous muscles, as well as the presence of additional mass lesions in the area of the scapular notch — the ganglionic cysts, tumors etc. [23, 24]. For the MRI, the pathognomonic signs shall include the swelling in the area of the supraspinal and the infraspinous muscles, the fatty degeneration, the presence of fluid-containing lesions in the area of the supraspinal scapular notch [23, 25, 26].

When suspecting the presence of the suprascapular nerve compression syndrome, electroneuromyography (ENMG) should be arranged. The main difference in cases of neuropathy is the presence of fibrillations and pathological fluctuations of the M-waves. ENMG allows for detecting the changes in the nerve conductivity and it can indicate the muscle hypotrophy, however, in the differential diagnostics with other diseases of the shoulder, it can be ineffective. It is worth noting that in cases of long-term presence of chronic neuropathy, the ENMG method becomes impractical [27], for it does not allow for detecting the damage of smaller fibers or of a part of the nerve. In addition to that, the negative ENMG results cannot unambiguously rule out the diagnosis of suprascapular neuropathy in case of the presence of the corresponding clinical signs of it [28, 29].

Upon setting the diagnosis of suprascapular neuropathy, it is possible to conduct an ultrasound examination (USE) [26, 30, 31]. According to the data from publications, ultrasound examination is a good method of evaluating the muscle damage, allowing for detecting the damage of muscle fibers at various levels, however, when performing the differential diagnostics procedures, it is necessary to use MRI.

Treatment

Conservative therapy. The direct reasons of the neuropathy itself, as well as its combination with other pathological changes in the area of the shoulder joint, are the most important factors for selecting proper treatment [27]. The majority of authors tend to believe that the initiation of neuropathy treatment should be conservative if this disease (for example, neoplasms in this zone or scapular fractures) is not resulting from the pathological processes requiring surgical intervention [32]. If conservative therapy does not show results, surgical decompression of the suprascapular nerve is recommended. Nevertheless, the optimal duration of non-surgical treatment remains unclear [33]. The literature data indicate that conservative therapy often has unsatisfactory results in patients with the duration of symptoms being more than half a year, as well as in the individuals with pronounced hypotrophy and atrophy of muscles, with space-occupying lesions and massive rotator cuff tears.

The reasons by which the status of the patients gets improved in cases of conservative therapy are not clearly identified: most probably, they can be related to the compensatory mechanisms in other shoulder girdle muscles [32].

Surgical treatment. The indication for surgical treatment include the compression of the nerve with space-occupying lesions, the massive rotator cuff tears, as well as the inefficiency of conservative therapy [32]. It was proven that, in patients with suprascapular neuropathy caused by the compression with soft tissues, surgical treatment provides better results, and, if possible, priority shall be given to arthroscopic intervention, not to the open-access methods [18, 34]. According to the modern outlooks, direct arthroscopic intervention [35–37] is the gold standard of treatment for suprascapular neuropathy [27, 36, 38], as well as for the concomitant diseases of the rotator cuff [23, 39, 40].

According to the data from modern publications, there is no unambiguous opinion on whether the arthroscopic decompression is indicated to patients with massive rotator cuff tears. Previously, the literature sources were reporting the improvement of the functional parameters in patients with massive rotator cuff tears combined with arthroscopic release of the suprascapular nerve. L. Lafoss et al. [34] have analyzed the results of arthroscopic decompression in a series of 10 patients and revealed an improvement of the status and the functions in all the patients. J.G. Costouros et al. [39] reported about six patients with neuropathy associated with vast rotator cuff rupture. The authors have found a stable improvement of the functions in four patients and partial restoration in two. In the research by A.A. Shah et al. [40], 21/24 (87.5%) of patients had deep pain in the posterior part of the shoulder and suprascapular neuropathy according to the data from ENMG. After the decompression of the suprascapular nerve, 17/24 (71%) of patients in 9 weeks after surgery had their pain intensity decreased with improving the parameters of the scale designed by the American Shoulder and Elbow Surgeons (ASES). However, in a series of 75 patients with massive ruptures of the rotator cuff, in which surgeries were conducted for restoring the integrity of the rotator cuff, L. Lafoss et al. [34] have revealed concomitant suprascapular neuropathy by means of ENMG before surgery in 29 (39%) cases. In this group, there were no statistically significant differences detected between patients with the nerve release and the ones not undergoing such an intervention.

The groups of P. Collin [29] and P. Yang [41] have reported that, among the patients with arthroscopic release of the suprascapular nerve combined with suturing the rotator cuff, there was no statistically more significant decrease in the pain syndrome, assessed using the visual analogue scale (VAS), comparing to the group of patients not undergoing arthroscopic release of the suprascapular nerve, i.e. with only suturing the rotator cuff. Besides, in the decompression group, there was no observed significantly better improvement in the values of patient status evaluation and in the range of motions in the shoulder joint assessed using the UCLA tool comparing to the group without the arthroscopic release of the suprascapular nerve. The research results have demonstrated that additional release of the suprascapular nerve does not bring additional benefit to the arthroscopic surgery aimed at restoring the rotator cuff and that the rate of developing neuropathy in the suprascapular nerve among the patients with ruptures in the posterior-upper part of the rotator cuff is 8.7%.

N.P. Sachinis et al. [27] have arranged a randomized controlled research to find out if the elimination of rupture itself represents a successful treatment method even in patients with diagnosed suprascapular neuropathy. The authors did not find significant differences in the improvement of shoulder functions between eliminating only the rotator cuff tear and fixing the rupture with an additional option of releasing the suprascapular nerve. Besides, the research has shown that shoulder function is inversely proportional to the fatty infiltration in the area of the

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subscapular muscle, which can develop secondary in terms of suprascapular neuropathy.

In the research by K. Yamacado [37], consisting of 31 cases of suprascapular neuropathy combined with rotator cuff tears, no significant differences were detected between the groups with releasing the suprascapular nerve and without it — by all the measurements applied during the final follow-up visit: the parameters of the UCLA and VAS scales did not show statistically significant difference among the two compared groups, however, the results have demonstrated that arthroscopic release of the suprascapular nerve as an addition to the arthroscopic repair of the tendons ultimately leads to the recovery and to improving the status comparing to the pre-operational data.

The research by Dr. A.R. Ginniyatov et al. [36] has shown that the use of arthroscopic release of the suprascapular nerve combined with massive rotator cuff tear has significantly improved the status of the patients within the first three months comparing to the group without the release, along with the highest significance of the methods shown in cases of massive tears.

In turn, the systematic analysis by A.B. Sandler et al. [42] has demonstrated that releasing the suprascapular nerve in the treatment of suprascapular neuropathy improves the functional results, however, more attention should be paid to the clinical symptoms and to the diagnostics of this disease.

Thus, it can be stated that the recent publications describe various results: some research works show the absence of statistically significant difference in the clinical results of reconstructing the rotator cuff with conducting the procedure of arthroscopic release and without it, while the others show positive results of arthroscopic release of the suprascapular nerve combined with suturing the rotator cuff. It is worth noting that the sample used in the proprietary research by the authors was small.

CONCLUSION

The conducted literature analysis has shown that, in cases of isolated suprascapular neuropathy, the majority of authors tend to conservative therapy, while in cases of abnormalities in the rotator cuff, all the researchers point out the necessity of surgical treatment. Despite the fact that the relation between the suprascapular neuropathy and the rotator cuff tears in the majority of research works is undoubtful, just as the fact that the combination of arthroscopic release of the suprascapular nerve together with the reconstruction of the rotator cuff provides good clinical and functional results, there is no unified opinion on the efficiency of the arthroscopic release of the suprascapular nerve. Publications exist that show the positive results of arthroscopic suprascapular nerve release in cases of a combination with massive rotator cuff tears (especially with the presence of neoplasms in the area of the scapular notch), however, according to the data from other investigators, statistical difference between restoring the rotator cuff with or without the release procedures was not detected. Thus, probably, a more strict limitation is required for the indications to arthroscopic release of the suprascapular nerve in case of its neuropathy based on the data obtained from the research works including larger patient samples.

ADDITIONAL INFORMATION

Author contributions. *O.G. Ushkova*, *A.M. Shershnev*, *V.I. Kuzmina*: search and review of literature, analysis of the data obtained, description of the results obtained; *S.Y. Dokolin:* control and editing of materials. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Pneumonitis as a Complication of Immunotherapy of Oncological Diseases: Difficulties in Diagnosis and Treatment

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ABSTRACT

Pneumonitis is one of the life-threatening complications of immunotherapy of oncological diseases. Despite the low occurrence rate, pneumonitis significantly affects not only the quality of life in the patients, but also the mortality, forcing to change the treatment scheme of the main disease. Therapy with immune checkpoint blockers is a relatively new, but well established type of oncology therapy. It is expected that, with the extension of the list of indications to immunotherapy, some growth would be observed in the number of complications, due to which it becomes necessary to inform the physicians of various (not only oncological) specialties about it. It is important for them to maintain high index of suspicion to be able to detect this life-threatening complication at the early stages and to prescribe adequate treatment. The currently known research works by national and foreign authors on the detection and treatment of pneumonitis in their majority have a strictly specialized type due to studying a specific immunotherapy medicine or a specific location of the tumor. In the present article, we have summarized and systematized the data from various sources, emphasizing on the diagnostics and therapy of this dangerous complication.

Keywords: *immunotherapy; checkpoint inhibitors; pneumonitis; computed tomography.*

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INTRODUCTION

Pneumonitis (pulmonitis) is a general term defining the inflammation of the pulmonary tissue, which, in case of bacterial or viral etiology, bears the name of pneumonia, while in the non-infectious origin of the disease (for example, after the exposure to allergic agents, radiation or medicinal products), a term “pneumonitis” is used.

Currently, the therapy with immune checkpoint blockers becomes more and more demanded, with this, the immunotherapy, just like any other treatment, has its side effects. The occurrence rate of such a life-threatening complication as pneumonitis, is small and ranges within 3–5% for cases of monotherapy with an inhibitor of the PD-1 (programmed cell death protein 1) or the PD-L1 (programmed death-ligand 1), reaching up to 10% in cases of combined therapy, however, according to the American Thoracic Society, the mortality rates reach 35% of the total number of fatal outcomes [1].

PATHOGENESIS OF PNEUMONITIS

The tumor cells at their core represent a foreign agent, even considering its development from the proprietary cells [2], which the immune system should recognize and destroy. However, to avoid death, the tumor cells have developed various protection mechanisms. The first way is the expression of cytotoxic CTLA-4 (cytotoxic T-lymphocyte associated protein 4) on their surface, which leads to the inhibition of the immune response [3]. The second is producing the PD-L1 and PD-L2 ligands, which bind to the PD-1 receptors on the T-cells, by this blocking them and restricting the immune reactions.

The immunotherapy is aimed at turning off the abovementioned mechanisms of inhibiting the immune system. By bonding to the cancer cells or lymphocytes, monoclonal antibodies to the immune control points block the interaction between the receptors, restoring the normal immune reaction. Currently, for clinical use,

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Пневмонит как осложнение иммунотерапии онкологических заболеваний: сложности диагностики и лечения

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АННОТАЦИЯ

Пневмонит — одно из жизнеугрожающих осложнений иммунотерапии онкологических заболеваний. Несмотря на низкую встречаемость, пневмонит оказывает значительное влияние не только на качество жизни пациентов, но и на смертность, в том числе заставляя менять схему лечения основного заболевания. Терапия ингибиторами контрольных точек иммунного ответа является относительно новым, но хорошо зарекомендовавшим себя видом лечения злокачественных новообразований. Ожидается, что с расширением списка показаний к иммунотерапии будет расти и количество осложнений, в связи с чем становится очевидной необходимость информирования об этом врачей разного (не только онкологического) профиля. Важно поддерживать у них высокий индекс подозрительности, чтобы на ранних этапах выявлять жизнеугрожающее осложнение и назначать адекватное лечение. Известные в настоящее время исследования отечественных и зарубежных авторов по выявлению и лечению пневмонита в большинстве своём носят узконаправленный характер, рассматривая конкретный препарат иммунотерапии или конкретную локализацию опухоли. В представленной статье мы объединили и систематизировали данные разных источников, делая акцент на диагностике и терапии этого опасного осложнения.

Ключевые слова: *иммунотерапия; ингибиторы контрольных точек; пневмонит; компьютерная томография.*

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the PD-1 inhibitors Nivolumab and Pembrolizumab are approved, as well as the PD-L1 inhibitors Atexolizumab, Avelumab and Durvalumab along with the CTLA-4 antibody Ipilimumab.

The pathogenesis of pneumonitis itself is not completely studied. According to one of the versions, the most substantial from our point of view, the immune checkpoints participate not only in the activation of the immune response, but also in the prevention of its excessive activity in terms of proprietary cells. In cases of immunotherapy, this mechanism gets turned off and the autoimmune processes develop.

RISK FACTORS OF DEVELOPING PNEUMONITIS

Pneumonitis, as a complication of immunotherapy, develops relatively infrequently, thus, there are circumstances increasing this probability. From various literature sources, we have isolated the main risk factors: the most commonly mentioned are the chronic diseases of the lungs in patients before treatment, such as the interstitial lung diseases, the chronic obstructive pulmonary disease, smoking, the combination with immunotherapy agents and other treatment methods [4], elderly age [5], past episodes of radiation therapy [6]. Also, a dependence was also shown on the type of tumor [7]: in particular, in renal cell cancer and non-small cell lung cancer, the occurrence rate of developing pneumonitis is higher than in melanoma (4.4% and 1.4%, respectively). The immunotherapy medication also plays a role: thus, PD-1 inhibitors show higher pneumonitis rates comparing to PD-L1 inhibitors and higher rate of III or IV degree pneumonitis. The rate of developing pneumonitis is not dose-dependent [7], however, its cumulative pattern was reported, i.e. the rate is higher in cases of long-term treatment.

CLINICAL SIGNS OF PNEUMONITIS

During the analysis of literature sources, it was found that pneumonitis does not exhibit characteristic clinical symptoms, with the main complaints being shortness of breath, coughing, fever and chest pain; also, previously existing chronic lung disease add to the complexity, the exacerbations of which show similar manifestations.

Pneumonitis is defined by the following diagnostic parameters based on the criteria proposed by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) [5]:

1) inexplicable increase in the shortness of breath within the last 30 days;
2) data from computed tomography with new bilateral foci of induration of pulmonary tissue showing the consolidation or ground glass patterns;
3) absence of signs of pulmonary infection as a result of diagnostic bronchoalveolar lavaging, endotracheal aspiration or sputum bacterial culture combined with negative blood tests for other potentially infectious pathogens;
4) absence of signs of malignant cells in the fluid obtained after the bronchoalveolar lavaging performed for the purpose of ruling out the lymphatic pattern of cancer spreading;
5) ruling out the left-sided cardiac failure and other possible causes of acute respiratory insufficiency;
6) the interval between the last administration of systemic antitumor therapy and developing the clinical and radiology signs being less than 4 weeks.

According to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE, version 5.0) [8], several severity degrees of pneumonitis are known:

- Ist degree — asymptomatic with the absence of clinical signs or complaints in a patient: the changes can be found only based on the results of computed tomography (CT); only clinical or diagnostic follow-up is indicated;
- IInd degree — symptoms, insignificantly affecting the quality of life in a patient, requiring only limited medical intervention (medication therapy);
- IIIrd degree — intensive symptoms, restricting the everyday activities of the patient, requiring medicinal and oxygen therapy;
- IVth degree — life-threatening respiratory insufficiency, emergency medical intervention is indicated (for example, tracheotomy or intubation);
- Vth degree — severe respiratory insufficiency, lethal outcome.

DIAGNOSTICS OF PNEUMONITIS

The functional examination of the lungs is one of the early and sensitive methods for the diagnostic of pneumonitis, which can be revealed by a relative decrease in functional expiratory vital capacity of ≥10% from the baseline value, a decrease in the diffusion capacity of the lungs for carbon monoxide (DLCO) <60% of the reference, by a decrease of the walking distance down to <300 m along with the desaturation by <85% to the end of 6 minute walking test.

Bronchoscopy with bronchoalveolar lavaging shall be arranged at the early stages of examination to rule out the alternative diagnoses, such as pneumonia [3]; the lymphocytes count being >60% can indicate the presence of pneumonitis.

High-resolution computed tomography is the gold standard of detecting pneumonitis, of evaluating its progression or resolving. As can be stated from the abovementioned classification by NCI CTCAE (v. 5.0), at the 1st stage of the disease, the radiology abnormalities precede the development of complaints in patients, due to which it is important to figure out what the CT-changes look like. Sadly, but there are no specific radiology signs of pneumonitis. Summarizing the data from the analyzed sources, we have defined the main and the most commonly manifesting patterns, which were classified in accordance with international multidisciplinary classification of interstitial pneumonias from the American Thoracic Society / European Respiratory Society (ATS/ERS) [9]:

- the pattern of cryptogenic organizing pneumonia [3] visualized as focal consolidation with subpleural and/or peribronchial distribution and air bronchograms. The specific signs considered is the reverse halo (atoll sign) — foci of opacity (ground glass-type) at the center and consolidation along the periphery (Fig. 1);
- the pattern of non-specific interstitial pneumonia [10] visualized as confluent bilateral opacity (ground glass-type) and reticular changes predominantly in the peripheral and lower areas of the lungs in the lower lobes with pronounced traction bronchiectases and loss of the lower lobe volume. Other findings may include peribronchovascular distribution with preserved normal pulmonary tissue subpleurally (Fig. 2);
- the pattern of hypersensitivity pneumonitis [11] visualized as diffusely distributed induration of the pulmonary tissue (ground glass-type) with centrilobular nodules and “air trapping” upon exhaling (Fig. 3);

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- the pattern of acute respiratory distress-syndrome [10] visualized as diffuse or multifocal increase in the density of pulmonary tissue (ground glass-type) and consolidation, predominantly with anterior-posterior gradient distribution, as well as decreased lung capacity, dilation of bronchi and traction bronchiectases (Fig. 4).

Particularly complex is the diagnostics of pneumonitis in patients with past episodes of radiation therapy applied to the chest cavity organs, for they develop another type of pneumonitis — the radiation one. The X-ray signs of radiation pneumonitis are the following: focal consolidation of pulmonary tissue located approximately in the area of the high-dose irradiation, more commonly unilateral, affecting lesser number of the lung lobes and having a sharp margin, not corresponding to the normal anatomy of the lobe, while the drug-induced pneumonitis has a tendency towards being bilateral, affecting more lobes and rarely having a sharp margin [6].

Taking into consideration the complexity of diagnostics and evaluation of pneumonitis associated with immunotherapy, a necessity occurs for searching new approaches to the analysis of CT-images. We have found the data on their processing by means of using the artificial intelligence software. During the pandemic of pneumonia associated with coronaviral infection (COVID-19), the developers were teaching the artificial intelligence software to recognize and to evaluate the characteristic changes in the pulmonary tissue. Taking into consideration the fact that the basis of the radiology pattern of COVID-19 includes the interstitial changes, it also becomes possible to recognize pneumonitis [12]. The extrinsic value in using the artificial intelligence is represented by the quantitative evaluation of the extent of impaired pulmonary tissue, which allows for tracking the dynamic changes of the disease. From our point of view, the research works in this field are of significant interest.

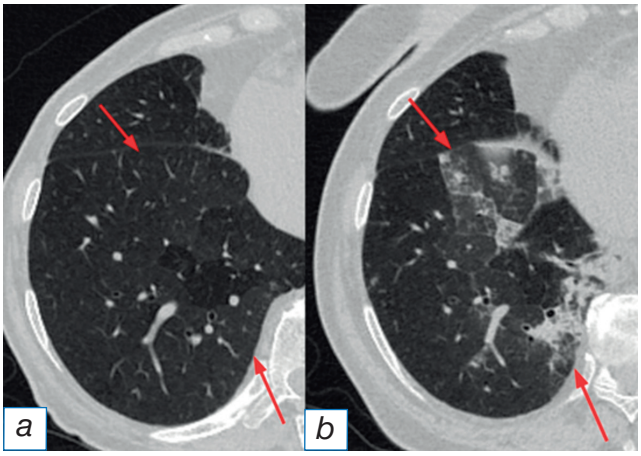

Fig. 1. The pattern of cryptogenic organizing pneumonia: before (*a*) and after (*b*) immunotherapy (arrows).

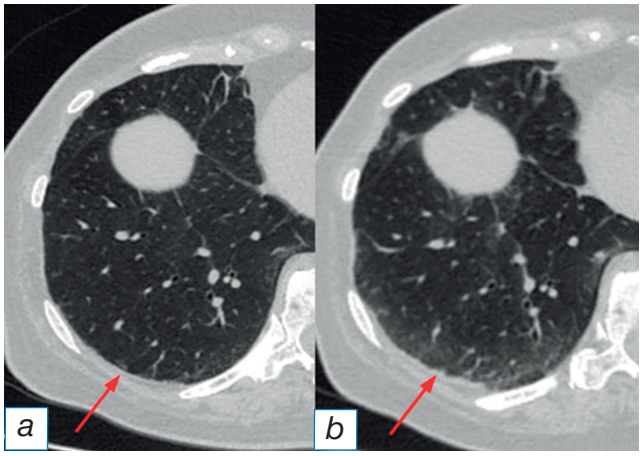

Fig. 2. The pattern of non-specific interstitial pneumonia: before (*a*) and after (*b*) immunotherapy (arrows).

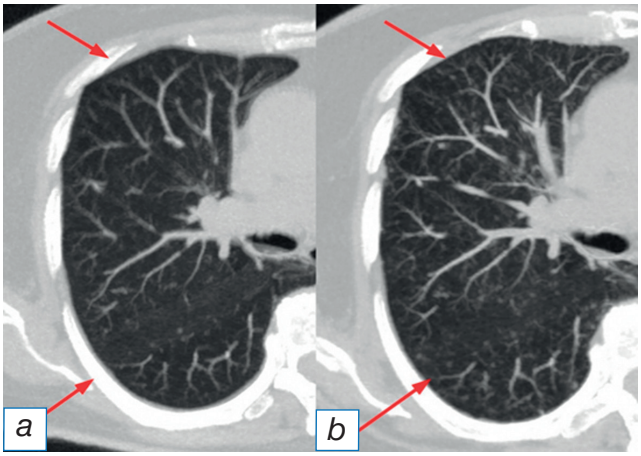

Fig. 3. The pattern of hypersensitivity pneumonitis: before (*a*) and after (*b*) immunotherapy (arrows).

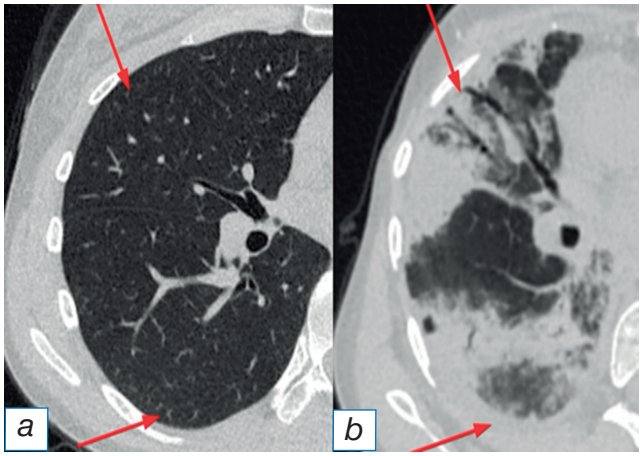

Fig. 4. The pattern of acute respiratory distress-syndrome: before (*a*) and after (*b*) immunotherapy (arrows).

TREATMENT OF PNEUMONITIS

The treatment tactics for pneumonitis in many sources is quite general by its nature. We have summarized the data from the national and foreign sources with systematizing them depending on the severity.

In case of grade I, no treatment is indicated, while the immunotherapy can be continued without interruption. The recommendations include regular check-ups with repeated chest CT scans and with testing the respiratory functions in 3–4 weeks. If clinical symptoms or radiology changes develop, which precede the progression of the disease, the treatment tactics shall be changed and shall correspond to higher grade pneumonitis.

In case of grade II, it is recommended to avoid continuing immunotherapy and to initiate oral glucocorticoids. Currently, there are no randomized clinical studies, which could show unambiguous approaches in terms of the dosages of systemic glucocorticoids and to the duration of their administration. Thus, in a small number of published articles [13], the dosages 1–2 mg/kg of the body weight for glucocorticoids were reported, the duration of therapy was 6–8 weeks (with maximum of up to 12 weeks). The national guidelines recommended Prednisolone at a dosage of 1–2 mg/kg daily or Methylprednisolone at a dosage of 0.5–1 mg/kg daily orally [14]. The treatment continues for 4–6 weeks. Generally, the patients are supervised in the out-patient settings with an evaluation of dynamic changes in the clinical signs within 48 hours from the initiation of steroid therapy and once or twice a week afterwards. The intake of glucocorticoids shall be continued at the initial dosage, until the symptoms do not regress to grade I or to the initial level, after which the dosage should be slowly decreased within a 6-weeks period.

In cases of grade III and IV pneumonitis, hospitalization is required with immediate cessation of immunotherapy. Before the initiation of therapy, bronchoscopy should be done with analyzing the bronchoalveolar lavaging sample for ruling out the infectious origin of the lesion. The majority of thoracic societies recommend intravenous injection of Methylprednisolone or its equivalent at high dosages (Methylprednisolone 1–2–4 mg/kg daily) [15]. The indication for oxygen therapy is the decrease of saturation to 88%.

Special attention should be paid to the fact that achieving clinical improvement in cases of glucocorticoid therapy is the signal to initiate the slow (lasting 6 weeks at least) decreasing the dosages of the medicinal product. In case of a rapid dosage decrease, ricochet pneumonitis develops, the course of which can be more severe than the one of the initial cases.

Particularly complex in terms of treatment is the steroid-refractory pneumonitis, which, according to the publication data, develops in 20–40% of the patients [13]. In case of developing the refractory pneumonitis, the options for consideration include additional immunosuppressive therapy with Mycophenolate Mofetil, Cyclophosphamide or Infliximab (5 mg/kg, single administration) [14, 15]. The intravenous therapy with immunoglobulins is proposed as the safer and more effective therapy than treatment with Infliximab or its combination with Immunoglobulin [13].

Another therapy option is the inhibitor of interleukin 6 receptors Tocilizumab, which has shown good efficiency in a single research. Other immunosuppressants, such as Mycophenolate Mofetil or Cyclophosphamide, are considered slow-acting, due to which their efficiency is doubtful.

According to the data from another research [4], the improvement/resolving of pneumonitis during the treatment can be achieved in 88–90% of the cases: for grade I — approximately in 100%, for grade II — in 93%, for grade III and higher — in 64%. This statistics shows the importance of detecting pneumonitis at early stages. However, even in cases of complete recovery, the overall survival of the patients having an episode of pneumonitis is lower comparing to the patients without such a complication [5].

In some research works, it was found that patients, in which adverse reactions develop, show better treatment response than in patients with no complications. Thus, the patients with pneumonitis have achieved higher rates of total treatment response comparing to the ones without it (37% versus 18%, respectively) [16]. Thus, re-initiation of immunotherapy can be desirable, though the total rates of side effects in cases of re-initiation are higher. According to the opinion from the Society for Immunotherapy of Cancer (SITC) [17], repeated intake of the medicine is possible in patients with completely treated pneumonitis grade II, as well as in separate patients with completely resolved grade III pneumonitis, in which the benefits of immunotherapy overwhelm the risk of recurrence-related complications. Patients with grade IV pneumonitis should not undergo repeated immunotherapy. In the national recommendations [14], it is permitted to re-initiate therapy for grades I and II, while grades III and IV mean permanent cessation of therapy.

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CONCLUSION

When selecting the articles and recommendations, we have grouped the data on the treatment of pneumonitis depending on the stage and we have reviewed the rarely used medicinal products. The analysis of a large number of literature sources helped us revealing the difficulties of this potentially fatal disease. One of the new and, from our point of view, promising methods is using the artificial intelligence for analyzing the CT-scans. The extrinsic value is shown for the possibility of quantitative evaluation of the impaired pulmonary tissue for more precise tracking of dynamic changes of the disease course.

Therapy with immune checkpoint blockers is a relatively new, but well-proven type of treatment for oncological diseases. Due to the fact that immunotherapy becomes more sought-after, currently even the list of indications used for this purpose becomes expanded, which, undoubtedly, shall lead to the growth in the number of complications and, due to the fact that such patients are admitted not only to the oncology-specialized institutions, a necessity grows in informing the physicians of various specialties in this threat. It is important to have the physicians maintaining a high index of suspicion, for pneumonitis is a life-threatening complication, nevertheless, when detected at early stages and with proper therapy prescribed, it is can be very successfully treated, which increases the survival rate among the oncology patients.

ADDITIONAL INFORMATION

Author contributions. *Yu.S. Chizhova:* review of publications on the topic of the article, writing the text of the manuscript; *V.D. Fedotov:* review of publications on the topic of the article, editing the manuscript; *E.M. Zakharova:* review of publications on the topic of the article. The authors confirm that their authorship complies with the international ICMJE criteria (all authors have approved the manuscript and also agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy and integrity of any part of it are appropriately reviewed and resolved).

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Difficulties in the Diagnostics of Transthyretin Amyloidosis with Polyneuropathy: a Clinical Case Description

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ABSTRACT

BACKGROUND: *In clinical practice, diagnosing of systemic transthyretin amyloidosis (ATTR-amyloidosis) with the impairment of the nervous and cardiovascular systems became possible due to the accessibility of genetic diagnostics and due to the growth of knowledge on this disease.* ***CLINICAL CASE DESCRIPTION:*** *A clinical case is presented of transthyretin amyloidosis, manifesting as polyneuropathy with significant neuropathic pain syndrome, with the development of severe vegetative insufficiency and with the impairment of the cardiovascular system in a 63 years old male. This clinical pattern, developing for 3 years, was associated with multiple encounters of the patient to various specialists — rheumatology physicians, neurosurgery specialists, endocrinologists, neurologists, internists, including surgical interventions in the spinal cord, carotid artery and cardiac vessels. The disease has lead to the development of severe cachexia and incapacitation of the patient.* ***CONCLUSION:*** *Taking into consideration that ATTR-amyloidosis manifests with the clinical signs of lesions in various organs and systems, and this is interpreted by the specialists within the framework of their specific field apart from the general etiology of the disease. The patient gets prescribed with multiple examinations and symptomatic medications, which causes a delay in the diagnostics and in setting the correct diagnosis. This clinical case describes the classical form of transthyretin amyloidosis, which, upon timely diagnostics, has its pathogenetic therapy.*

Keywords: *transthyretin amyloidosis; polyneuropathy; vegetative dysfunction; orthostatic hypotension; clinical case.*

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BACKGROUND

Transthyretin amyloidosis (ATTR-amyloidosis) is a rare disease with irreversibly progressive course due to the accumulation of the pathological protein — the transthyretin (TTR) in the peripheral nervous system, kidneys, heart, intestines and other organs [1–3].

The protein name “transthyretin” (transports thyroxine and retinol) is related to the transportation of the thyroid gland hormone thyroxin (T4) and retinol upon binding to the retinol-binding protein in the target organs for normal functioning. Up to 95% of transthyretin is synthesized by hepatic cells and secreted into the circulation [4, 5], with the remaining part being produced in the vascular plexus of the brain and in the pigmented epithelium of the eye retina and it circulates in the cerebrospinal fluid, not reaching the circulation. The TTR secretion begins in the process of embryonic development and continues throughout the entire life. The blood concentration of transthyretin is minimal in neonates, but with ageing, an increase develops in the levels of this protein with its gradual decrease after the age of 50 years [6].

The most common cause of ATTR-amyloidosis is the mutation in the *TTR* gene, resulting in an impaired secondary and tertiary structure of the TTR protein: in cases of the pathological type, transthyretin does not reproduce its usual tetrameric form, but forms the amyloid fibrils. The accumulated TTR-protein affects the operation of the cell with its further death [1, 3].

The first clinical course of familial transthyretin amyloid polyneuropathy was described in 1952 by the Portuguese Neurologist C. Andrade in patients from Northern Portugal, and later on, due to the development

Сложности в диагностике транстиретинового амилоидоза с полинейропатией: клинический случай

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АННОТАЦИЯ

Обоснование. *В клинической практике диагностирование системного транстиретинового амилоидоза (ATTR-амилоидоз) с поражением нервной и сердечно-сосудистой систем стало возможным благодаря доступности генетической диагностики и увеличению знаний о данной патологии.* ***Описание клинического случая.*** *Представлен клинический случай транстиретинового амилоидоза, проявляющегося полинейропатией с выраженным нейропатическим болевым синдромом, развитием грубой вегетативной недостаточности и поражением сердечно-сосудистой системы у мужчины 63 лет. Данной клинической картине, развивавшейся в течение 3 лет, сопутствовали многочисленные обращения пациента к различным специалистам — ревматологам, нейрохирургам, эндокринологам, неврологам, терапевтам, в том числе оперативные вмешательства на спинном мозге, сонной артерии и сосудах сердца. Заболевание привело к выраженной кахексии и инвалидизации пациента.* ***Заключение.*** *ATTR-амилоидоз проявляется поражением различных органов и систем, и это воспринимается врачами-специалистами в рамках своей области в отрыве от общей картины заболевания. Пациенту назначаются многочисленные исследования и симптоматические препараты, что вызывает задержку в диагностике и постановке правильного диагноза. Данный клинический случай описывает классическую форму транстиретинового амилоидоза, которая при своевременной диагностике имеет патогенетическое лечение.*

Ключевые слова: *транстиретиновый амилоидоз; полинейропатия; вегетативная дисфункция; ортостатическая гипотензия; клинический случай.*

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of genetic diagnostics, this neurodegenerative disease was diagnosed worldwide [1, 7].

The incidence of developing the transthyretin amyloidosis is variable depending on the regions, even among the members of one family. Taking into consideration the incomplete penetrance, the individuals bearing the pathological gene can live long enough without clinical manifestations of the disease [5]. The average life expectancy from the moment of clinical manifestations until the lethal outcome for TTR-amyloidosis is 15 years, but these ranges can vary depending on the genotype, the age of disease onset, the clinical signs and the place of residence [2].

TTR-amyloidosis represents in two forms [3] — the acquired one (caused by the abnormal accumulation of wild type transthyretin) and the hereditary form (more than 140 variants of mutations in the *TTR* gene).

The clinical manifestations of transthyretin amyloidosis include the polyneuropathy with severe pain syndrome; the carpal canal syndrome; the dysfunction of the vegetative nervous system of unclear etiology (erectile dysfunction, orthostatic hypotension, impaired motor activity of the gastrointestinal tract, cardiac rhythm disorder); cardiac impairment with an enlargement of the walls in the right and left ventricles in the absence of arterial hypertension and combined with orthostatic hypotension [1, 3, 7].

Predominantly, the first manifestation of TTR-amyloidosis is the polyneuropathic syndrome, less frequently — the vegetative disorder. In 18% of the

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cases amyloidosis affects the heart, which results in rhythm abnormalities, requiring the installation of the pacemaker [1, 3].

TTR-amyloidosis was considered an incurable disease until the development of the first liver transplantations in 1990-s [1]. As of today, the pathogenetic therapy of transthyretin amyloidosis for the purpose of stabilizing the TTR-tetramers is carried out using the medicinal agents Diflunisal and Tafamidis [5]. Diflunisal, being a drug product from the group of non-steroid anti-inflammatory medications, affecting the foci of T4 binding at the TTR, slows down the process of amyloidogenesis [5, 8], however, taking into consideration the negative effects on the side of the gastrointestinal tract, for 57% of the patients, this medicine is currently not approved for use (research works are pending) [8]. Tafamidis stabilizes the TTR tetramer by means of binding to the thyroxin-binding site of the TTR, both the wild type and the mutated one [8, 9]. In patients with the manifestation of clinical signs at the age of <50 years, Tafamidis was decreasing the risk of mortality comparing to the risk for the patients not receiving therapy by 91%, while among the individuals with the onset of the disease at ≥50 years of age — by 82% [9].

CLINICAL CASE DESCRIPTION

Patient info

Patient named M., aged 63 years, a retired resident of the city of Tyumen, was admitted in June 2024 to the Neurology Department of the State Budgetary Healthcare Institution of the Tyumen Oblast "Regional Clinical Hospital No. 1" (RCH No. 1 of the city of Tyumen) with the complaints of weakness and pain in the muscles of the limbs, pain in the vertebral column, dizziness, generalized weakness, frequent loose stools and impaired erectile functions.

Case history. From 2020 (at the age of 59 years), the patient started noting weakness and prickling in his upper and lower limbs, intensive pain in the limbs and in the vertebral column, decreased blood pressure (down to 90/60 mm.Hg.) along with erectile dysfunction. From November 2021, headaches and dizziness have also developed.

Due to the persisting pain syndrome, on 25.01.2022 the patient was examined by the Rheumatologist, no abnormalities were detected. One and a half year from the moment of the clinical manifestations, the patient had lost 20 kg of body weight. From February 2022, shortness of breath started developing upon physical activity: the coronary angiography on 03.08.2022 has shown no abnormalities. In July 2022, carotid endarterectomy was arranged on the right side due to the hemodynamically significant stenosis of the internal carotid artery — down to 85%.

From 19.09.2022 until 29.09.2022, the patient was staying at the Neurosurgery Department of the Federal Center for Neurosurgery of the city of Tyumen with the complaints of pain and numbness in the upper and lower limbs, pain in all the segments of the vertebral column. Objective assessment has revealed the "gloves and socks" hypesthesia, significant tremors in the distal segments of the upper limbs. Clinical hematology panel: mild anemia (Red blood cells 3.63×10^{12}/l, hemoglobin 108 g/l). Magnetic resonance tomography of the cervical, thoracic and lumbar spine on 19.09.2022: arthrosis of the facet joints, mild central stenosis at the level of C6–C7, moderate — at the levels C4–C6 and Th10–Th11. Moderate bilateral foraminal stenosis at the level of C4–C7. Electrocardiography was conducted on 19.09.2022: sinus rhythm with a heart rate of 77 bpm, left anterior fascicular block, signs of loading in the right atrium. On 23.09.2022, a decision was drawn up on arranging the temporary epidural electrostimulation of the spinal cord at the level of C3–C5. The postoperative period was unremarkable (no complications), weakly positive effect was reported.

From 02.11.2022 until 11.11.2022, the patient was receiving scheduled treatment at the Cardiology Department of the Tyumen RCH No. 1.

Laboratory and instrumental diagnosis

On 07.11.2022, the transluminal balloon angioplasty and stenting of the coronary artery were performed. The postoperative period was unremarkable (no complications). The clinical hematology panel was showing persisting anemia (Red blood cells 3.41×10^{12}/l, hemoglobin 92 g/l). Echocardiography on 11.12.2022: atherosclerosis of the aorta, insignificant myocardial hypertrophy of the left ventricle, insignificant amount of fluid within the pericardial cavity.

From 27.12.2022 until 04.01.2023, the patient underwent in-patient treatment at the Endocrinology Department. Upon visual examination, the body weight was 40 kg, height — 168 cm, body mass index (BMI) — 14.17 kg/m^2. The blood cortisol concentration was less than 1 μg/dl (ref. range: 3.7–19), adrenocorticotropic hormone — 2.3 pg/ml (ref. range: 7.2–63.8). The diagnosis set was the secondary insufficiency of the adrenal cortex, the intake of Prednisolone was recommended at a dosage of 5 mg daily.

On 08.01.2023 — transported by the ambulance crew to the Tyumen RCH No. 1 with arterial hypotension (blood pressure — 50/35 mm.Hg.) and complaints of severe weakness, prickling and numbness in the upper and lower limbs, severe dizziness and shortness of breath on minimal physical loading.

Clinical hematology panel: Red blood cells 3.65×10^{12}/l, hemoglobin 108 g/l with a decrease of serum iron concentration down to 7.7 mmol/l. The blood biochemistry panel and the clinical urinalysis were unremarkable. The C-reactive protein level was normal. The parathyroid and the thyroid-stimulating hormones, the Free T4, the luteinizing and the follicle-stimulating hormones were normal, as well as the levels of cortisol. Decreased blood testosterone was found — down to 3.1 ng/ml. Upon the ultrasound examination of the thyroid gland, kidneys and adrenal glands — no abnormalities were detected. Electrocardiography on 10.01.2023: sinus rhythm with a heart rate of 89 bpm, left anterior fascicular block, signs of loading in the right atrium, signs of hypertrophy in the left ventricle. Electroneuromyography on 12.01.2023: signs of sensory-motor polyneuropathy in the lower limbs, predominantly of axonal type. X-ray densitometry on 12.01.2023: the lumbar segment of the vertebral column and the femoral neck show decreased mineral density down to the level of osteoporosis (T-Student's test -2.9 SD and -3.3 SD respectively). Ultrasound duplex scanning of the brachiocephalic arteries on 13.01.2023: atherosclerosis of the brachiocephalic arteries, stenosis down to 45–50%. Computed tomography of the chest cavity organs: signs of insignificant mixed-type emphysema. The patient was discharged in generally satisfactory status with stable hemodynamic parameters.

On 20.06.2023, due to the persisting pain syndrome in the back and limbs along with the numbness in the upper and lower limbs, the patient was repeatedly admitted to the Neurosurgery Department of the Federal Center for Neurosurgery of the city of Tyumen, where he once again underwent an implantation of the system intended for epidural electrostimulation of the spinal cord at the level of C3–C5 vertebral bodies.

Conclusion on the electroneuromyography examination of the upper and lower limbs (self-encounter due to the persisting numbness in the limbs): signs of significant motor-sensory axonal-demyelinating polyneuropathy of the limbs with an accent in the lower ones. The amplitude of the motor and sensory responses is significantly decreased (>96%). The rate of conduction of excitation in the peripheral nerves is decreased in the upper (by 25–30%) and in the lower (35–50%) limbs.

Physical diagnostics. Body weight 40 kg. Height 168 cm. BMI 14.17 kg/m^2. General status — satisfactory. Heart rate — 62/minute. The pulse is rhythmic. Blood pressure in the right arm — 86/60 mm.Hg. in the horizontal position, 55/40 mm.Hg. in the vertical position, in the left arm — 74/50 mm.Hg. in the vertical position. The heart tones are muffled but rhythmic.

Neurological status. The critical thinking is intact. The oculomotor nerves show no abnormalities. The face is symmetrical. Primitive oral reflexes: snout reflex. The soft palatine and the gag reflexes are intact. The muscle strength in the upper limbs — proximally 4 points, distally — 2–3 points. The muscle strength in the lower limbs is proximally 3–4 points, distally — 2 points. The muscle tone in the limbs is decreased. Atrophy in the muscles of the hypothenar, thenar, trapezius muscles of the shoulder joint, in the thigh and shin muscles. Fascicular tremors were revealed in the muscles of the shoulder girdle. The reflexes in the upper limbs are active in the biceps and triceps muscles, no carpal reflexes were observed. The reflexes in the lower limbs: knee and Achilles tendon — none on both sides. Pathological plantar reflexes — absent. Romberg stance test shows sensitive ataxia. Coordination tests — an intention tremor was detected on both sides. Hypoaesthesia up to the upper third of the forearm, down to the lower third of the thighs. Paraesthesias in the lower limbs. The functions of the pelvic organs are properly controlled.

Provisional diagnosis

Axonal type polyneuropathy, unspecified.

Genetic examination

Taking into consideration the clinical signs and the case history, the patient had his blood sample drawn for conducting the genetical testing for the purpose of ruling out the transthyretin amyloidosis, and on 30.04.2024, using the Sanger sequencing method, a pathogenic mutation was detected in exon 2 of the *TTR* gene (Nm_000371.4) c.148G>A (p.Val50Met).

For the purpose of ruling out the amyloidosis with light chain amyloid (AL-type of amyloidosis), 24-hour samples of blood and urine were tested (21.06.2024): the concentration of immunoglobulins are within the normal ranges, no monoclonal secretion detected. Scintigraphy of the myocardium was arranged (21.05.2024): accumulation of the amyloid was shown in the heart, malignancy degree (Grade) III (Fig. 1).

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Main diagnosis

Transthyretin amyloidosis with polyneuropathy and amyloid lesions in the heart, grade III, severe sensitive ataxia, severe neuropathic pain syndrome, moderate flaccid tetraparesis.

Concomitant diagnoses. Secondary insufficiency of adrenal cortex. Orthostatic hypotension. Significant body weight deficit (BMI 14.17 kg/m^2). Adenoma of the prostate gland. Degenerative-dystrophic changes in the vertebral column, thoracalgia syndrome, lumboischialgia with stable bilateral pain syndrome, incomplete remission and chronic recurrent course. S/p implantation of the system for epidural electrostimulation of the spinal cord on 20.06.2023. Carotid endarterectomy of the internal carotid artery on 29.07.2022. Ischemic heart disease. Atherosclerosis of coronary arteries. Transluminal balloon coronary angioplasty with stenting the right coronary artery on 07.11.2022. Hypertensive disease stage III, risk 4, controlled. Chronic cardiac failure grade I, functional class II.

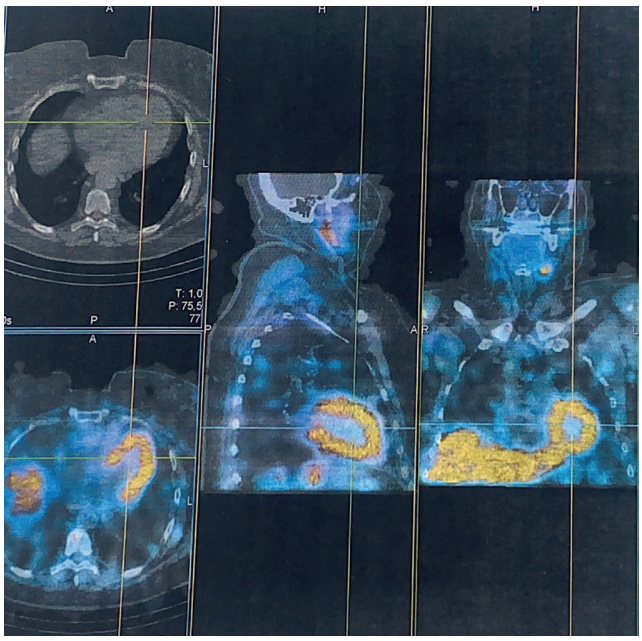

Fig. 1. Scintigraphy of myocardium: accumulation of amyloid in the heart, grade III of malignancy (Grade).

Follow-up and outcomes

The genetic testing of blood samples from the three sons of the patient shows that none of them is carrying a pathological variant c.148G>A (p.Val50Met) in the *TTR* gene, detected in their father.

The patient has received recommendations on taking the medicinal product Tafamidis 61 mg once daily, not crushing the pill and not cutting it, not related to the intake of meals.

DISCUSSION

Transthyretin amyloidosis is a multisystemic disease associated with the deposition of amyloid in the neural tissue, in the heart, the kidneys, the eyes and the gastrointestinal tract. Taking into consideration the polysystemic origin of the disease, amyloidosis often mimics the disease of the internal organs, due to which the clinical signs with the predominance of one or another complaints are investigated by various specialists (neurologists, cardiologists, endocrinologists etc.), which results in delayed setting the correct diagnosis, the progression of the disease with the development of decompensation in the organs and systems, delaying the initiation of the pathogenetic therapy and, as a result, the incapacitation of the patient with decreasing the quality of his/her life. In the endemic regions (Portugal, Sweden, Japan, Brazil, Cyprus, Majorca, Bulgaria), transthyretin amyloidosis is found with an occurrence rate of 1:1000, while in cases of hereditary ATTR-polyneuropathy, known in 36 countries of the world — in 1:1 000 000 of the population [10]. Setting the correct diagnosis in patients with amyloidosis takes an average of approximately three years [2], which is related to the absence of hereditary history, to multiple and non-specific clinical manifestations. The most frequent neurological diagnoses, which are set for the patients with ATTR-amyloidosis, include polyneuropathy of unspecified origin, chronic inflammatory demyelinating polyneuropathy, lateral amyotrophic sclerosis, degenerative-dystrophic changes of the vertebral column with radiculopathy and Parkinson disease [2].

Early diagnostics of ATTR-amyloidosis allows for prescribing the pathogenetic therapy (according to the vital indications) before the development of irreversible incapacitating changes in the organs and systems, the therapy that is aimed at preventing the accumulation of amyloid. In Russia currently there is a registered pathogenetic therapy medicine with proven efficiency — Vyndaqel (Tafamidis)[1], which selectively binds to the transthyretin protein, causing its stabilization and preventing amyloid deposition [11], by this significantly slowing the progression of neurological symptoms, preventing the loss of body weight in patients with ATTR-polyneuropathy, which is confirmed by the results of numerous observations

[1] Instructions on the medical application of Vyndaqel drug product. Access mode: https://grls.rosminzdrav.ru/GRLS.aspx?RegNumber=&MnnR=&lf=&TradeNmR=Виндакель&OwnerName=&MnfOrg=&MnfOrgCountry=&isfs=0&regtype=1%2c6&pageSize=10&token=7e96bd09-3b25-4dcf-a2b1-79aa4abc9c58&order=Registered&orderType=desc&pageNum=1

from foreign authors [8, 9, 11, 12]. In the presented clinical case, what calls attention to itself is practically four years of delayed period from the development of polyneuropathy symptoms and erectile dysfunction to setting the clinical diagnosis. The patient was supervised by the endocrinologists, rheumatologists, cardiologists, neurologists, he had twice underwent an invasive implantation of epidural electrodes due to his pain syndrome. Thus, the patient underwent multiple examinations and was repeatedly operated.

The provided observation demonstrates the irreversibly progressing type of the course of transthyretin amyloidosis with the dysfunction of the vegetative nervous system, expressed as the development of orthostatic hypotension, erectile dysfunction, impaired motor functions of the gastrointestinal tract with a background of completely intact cognitive functions. The accumulation of the modified amyloid has lead to the deficit of the body weight (BMI 14.34 kg/m^2), to the severe pain syndrome in the limbs, to difficulties in unassisted movement and to severe vegetative disorders. At the same time, the timely conducted genetic testing, setting the correct diagnosis and prescribing proper therapy could prevent the incapacitation of the patient.

CONCLUSION

Practicing physicians need to remember about ATTR-amyloidosis, the timely genetic diagnostics of which allows for prescribing the pathogenetic therapy, slowing down the progression of the disease and significantly improving the quality of life in a patient.

ADDITIONAL INFORMATION

Author contributions. *E.S. Ostapchuk:* review of publications on the topic of the article, scientific editing of the article; *O.P. Glinin:* description of the clinical case, review of publications on the topic of the article; *Yu.V. Alekseeva:* treatment of the patient, correction of the handwritten part of the text. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2024 July 8). The volume of published data was agreed upon with the patient.

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The Patient's Way to Diagnosis: A Clinical Case of Late Onset Pompe Disease in an Adult

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ABSTRACT

BACKGROUND: *Late onset Pompe disease is a rare genetic disease from the group of the accumulation diseases, the main manifestation of which is the progressive myopathic syndrome. The difficulties of diagnostics are mainly related to the low awareness of the specialized physicians (neurologists, orthopaedists, rheumatologists, pulmonologists, pediatricians etc.) on the specific features of this disease, as well as to the low level of nosological specificity of the myopathic syndrome in general. Special importance of early diagnostics is due to the existence of pathogenetic therapy. Late diagnostics and delayed initiation of therapy lead to lower survival rate and higher rate of incapacitation among the patients.* ***CLINICAL CASE DESCRIPTION:*** *The patient aged 62 years, which for many years was under the supervision by neurologists with the diagnosis of osteochondrosis, based on the objective data, actually had a myopathic syndrome that was diagnosed and confirmed using the electroneuromyography. The detected findings included a decrease in the activity of the alpha-glucosidase enzyme, while the genetic examination that followed, allowed for detecting the presence of a mutation in the GAA gene. The dynamic changes of the disease were tracked with a background of taking pathogenetic therapy for 4 years.* ***CONCLUSION:*** *This clinical case demonstrates the many years of the patient's way to being diagnosed with a rare genetic disease and, respectively, to the later initiation of therapy. The efficiency of treating the accumulation diseases directly depends on the extent of the pathological changes in the target organs, accumulated to the moment of diagnostics, which means — the earlier, the more effective.*

Keywords: *late onset Pompe disease; myopathy; enzyme replacement therapy; glycogenosis type II; accumulation diseases.*

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BACKGROUND

Late onset Pompe disease is a rare disease, which relates to type II glycogenosis and is a hereditary accumulation disease with an autosomal-recessive mode of inheritance. The clinical manifestations of the disease are determined by the accumulation of glycogen in the lysosomes of the skeletal muscles, of the parenchymatous organs, of the nervous system and of other tissues. The accumulation of glycogen is caused by the insufficiency of the enzyme — the acid alpha-glucosidase. The insufficiency of the enzyme develops as a result of *GAA* gene mutation (glucosidase alpha acid), localized at a long arm of the 17th chromosome.

The incidence of the disease in various countries ranges from 1:300 000 to 1:40 000 [1–3]. In Russia, the Pompe disease is included into the list of orphan diseases, but its incidence is unknown. As of the year 2024, in Russia this diagnosis was set to approximately 100 patients[1].

The majority of patients go through a very long way to setting the diagnosis and receiving the pathogenetic therapy. The low level of diagnostics is also due to the insufficient awareness of the pediatricians and neurologists on the specific features of the disease. The knowledge about this disease must also be available to the physicians of other specialties: pulmonologists, orthopaedists, rheumatologists and internists [4]. The difficulties of diagnostics are primarily related to the high variability of the disease onset age. Late onset Pompe disease can manifest both at an early age

[1] RG.RU [Internet]. Nevinnaya I. The experts: we need faster solving for the issue of including the Pompe disease into the neonatal screening // *Russian newspaper*. April 15, 2024. Access mode: https://rg.ru/2024/04/15/eksperty-nuzhno-bystree-reshit-vopros-s-vkliucheniem-v-neonatalnyj-skrining-bolezni-pompe.html

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Путь пациента к диагнозу: клинический случай болезни Помпе с поздним началом у взрослого

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АННОТАЦИЯ

Обоснование. *Болезнь Помпе с поздним началом — редкое генетическое заболевание, относящееся к болезням накопления, основным проявлением которого является прогрессирующий миопатический синдром. Трудности диагностики связаны в основном с низкой осведомлённостью врачей-специалистов (неврологов, ортопедов, ревматологов, пульмонологов, педиатров и др.) об особенностях этого заболевания, а также с низким уровнем нозологической специфичности миопатического синдрома в целом. Особая важность ранней диагностики обусловлена существованием патогенетической терапии. Поздняя диагностика и отсроченное начало терапии ведут к меньшей выживаемости и большей частоте инвалидизации пациентов.* ***Описание клинического случая.*** *У пациентки 62 лет, много лет наблюдавшейся у неврологов с диагнозом остеохондроза, объективно был выявлен миопатический синдром, подтверждённый с помощью электронейромиографии. Обнаружено снижение активности фермента альфа-глюкозидазы, а последующее генетическое исследование позволило определить наличие мутации в гене GAA. Прослежена динамика заболевания на фоне приёма патогенетической терапии в течение 4 лет.* ***Заключение.*** *Данный клинический случай иллюстрирует многолетний путь пациентки с редким генетическим заболеванием к диагнозу и, соответственно, более позднему началу терапии.*

Ключевые слова: *болезнь Помпе с поздним началом; миопатия; ферментозаместительная терапия; гликогеноз II типа; болезни накопления.*

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(after 1 year of age) and at the older age. The main problem of the diagnostics is the non-specificity of clinical manifestations, the phenotype of patients with late onset Pompe disease is similar to a large number of neuro-muscular diseases. Due to the fact that late onset Pompe disease belongs to the group of myopathies, among the clinical signs, the ones prevailing are the muscle weakness and the respiratory abnormalities, which slowly progress and do not show clear nosological specificity. The diagnostics of Pompe disease is based on the screening of the activity of the acid alpha-glucosidase enzyme[2], which is supported by the molecular-genetic testing of the *GAA* gene upon detecting the decreased activity of the enzyme [5–7].

All the patients with Pompe disease should receive lifetime pathogenetic enzyme replacement therapy. Currently, in the Russian Federation, two medicinal products are registered: Alglucosidase alfa (from 2013) and Avalglucosidase alfa (from 2023). Avalglucosidase alfa, according to the data from clinical research, is a more effective medicinal product with better safety profile [8].

CLINICAL CASE DESCRIPTION

Patient info

Female patient X. born in 1959, office worker. Presented to the Neuromuscular Diseases Office of the Consultative and Diagnostic Center of the Federal State Budgetary Scientific Institution “Scientific Research Institute for Complex Problems of Hygiene and Occupational Diseases” (SRI CPH and OD) in March 2021 with the complaints of weakness in the limbs;

[2] Ministry of Health of the Russian Federation. List of headings of the clinical recommendations [Internet]. Pompe disease. The Union of Pediatricians of Russia, the Association of Medical Geneticists, Society of Specialists on Neuromuscular Diseases, 2019. Access mode: https://cr.minzdrav.gov.ru/view-cr/317_1

difficulties when walking up (the stairs, in the transport vehicles, walking uphill); when standing from the sitting position or lying position; changes in the gait; periodical spasms in the gastrocnemius muscles; shortness of breath when walking and upon mild physical activity.

Case history. The early development of the patient was unremarkable. From the school age, she had noted problems during physical exercises at school: difficulties were experienced when jumping or running (the only "C" mark during the school years was for physical education). From 2004/ 2005 (at the age of about 45 years), she started noting difficulties when standing up from the squat on haunches, when walking up the stairs of the vehicle; slight limping has developed. After 3 more years, a clear gait change was observed. During the last year, shortness of breath developed. The disease course is progressing. The relatives had no such symptoms. From the age of 30 years, the patient periodically undergoes check-ups at the neurologist office due to osteochondrosis with short-term effect.

Regular medical check-ups (follow-up). Disability group II (mastectomy in 2005 due to the malignant neoplasm, radiation and chemotherapy were used); hypothyroidism from 2006 (replacement therapy — receiving Euthyrox at a dosage of 100 μg).

The presence of injuries or infectious diseases — negative (verbal information provided by the patient).

Laboratory and instrumental diagnosis

Objective findings: clear consciousness, adequate behavior; oriented in the location, time and personality. The body constitution is correct, normosthenic. Height 172 cm, weight 82 kg. The skin surface is clean, showing usual coloring. Breath rate — 18 per minute, no rales were found in the lungs. Upon auscultation, the heart tones are rhythmic, the heart rate is 75 bpm, the blood pressure level is 120/78 mm.Hg. The abdomen is soft and painless. The functions of the pelvic organs are not impaired.

Fig. 1. Gower's maneuver upon standing.

Trendelenburg gait, the patient experiences significant difficulties when standing up from the sitting position, from the lying position, from squat on haunches, using the Gower's maneuvers (weakness of axial muscles) (Fig. 1, Supplement 1).

Craniocerebral nerves: the patient is capable of differentiating the smells, the fields of vision upon quick testing are normal, the palpebral fissures and the pupils are equal, active photoreactions are present, the ocular motility has a full range, no signs of nystagmus were found, the facial sensitivity is not impaired, the face is symmetrical, the phonation is intact, the throat reflexes show medium degree of activity, the tongue is positioned along the midline, no fasciculations were noted (visible involuntary contractions in separate bundles of muscle fibers).

Muscles. Mimic muscles — 5 points of strength according to the MRC scale (Medical Research Council). Strength in the proximal segments of the upper limbs: 4–5 points, in the extensor muscles of the forearms — 4 points, in the proximal segments of the lower limbs — 3–4 points; more decreased strength of the extensors and the adductors of the thighs, along with the extensor muscles of the shins. Visually, there are no signs of muscle atrophy or pterygoid scapulas.

Reflexes. The tone in upper and lower limbs is decreased, the tendon reflexes in the upper and lower limbs are decreased, no pathological reflexes were found. The abdominal reflexes are decreased (flaccid anterior wall of the abdomen), no sensitive disorders were observed. Romberg stance test — stable, coordination tests — satisfactorily.

The specific complaints and data from the neurological assessment allowed for suspecting the presence of primary muscular disease.

The provisional diagnosis set was the following: "Myopathic syndrome of unclear origin".

Clinical blood and urine tests were showing no abnormalities, except for periodical elevation of creatinphosphokinase (CPK) from 300 to 500–600 U/l.

Data from stimulation electroneuromyography conducted on the day of presenting to the Clinic of the SRI CPH and OD in March 2021: the conduction of impulse in the nerves of the upper and lower limbs is not impaired. Upon the needle electromyography of the muscles of the upper and lower limbs, single spontaneous activity was registered in the proximal muscles, the movement unit potentials in the distal muscles are intact, in the proximal muscles of the upper (the deltoid) and lower limbs (the quadriceps, the femoral adductor), the movement unit potentials have moderate remodeling of muscle type expressed as a decrease in the mean duration (Fig. 2).

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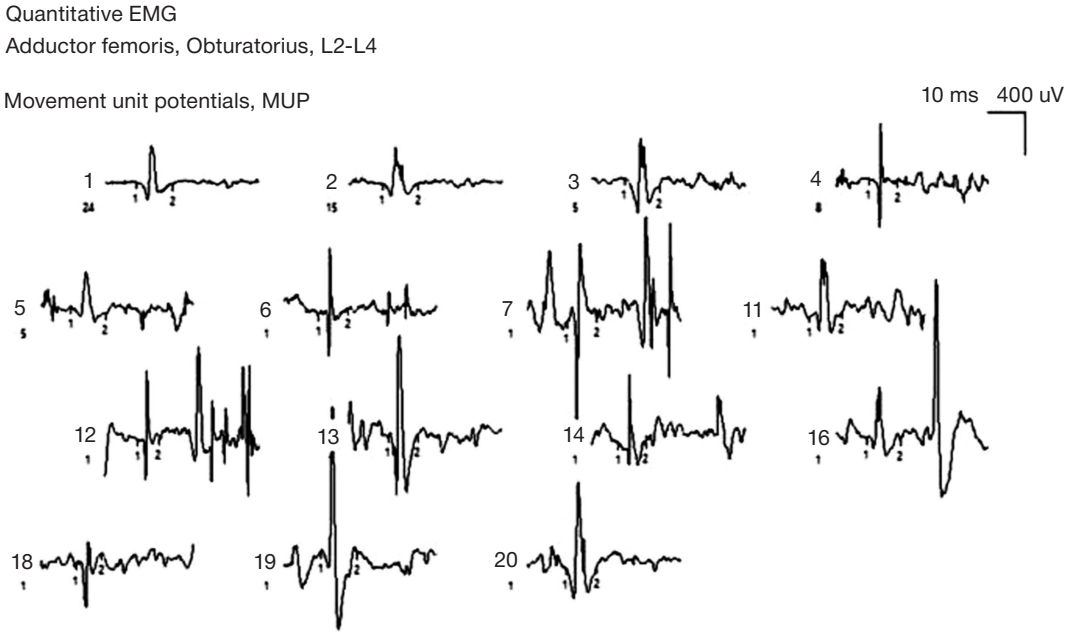
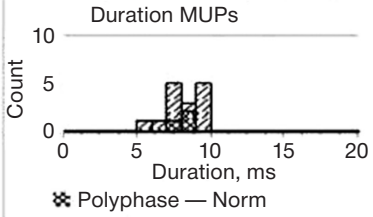


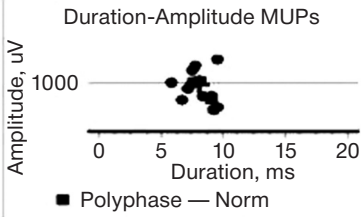
Duration MUPs

	Min duration, ms	Max duration, ms	Average duration, ms	Stage	Quantity MUPs
Total	5.8	9.48	8.08		15
N/p	5.8	9.48	8.05		12
P/p	7.52	8.98	8.19		3

Amplitude MUPs

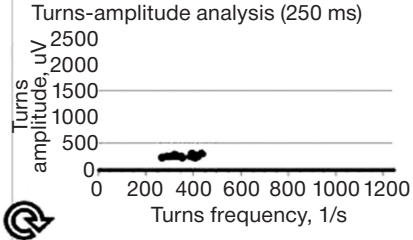
	Min amplitude, uV	Max amplitude, uV	Average amplitude, uV	Polyphase, %
Total	457	2057	940	20.0
N/p	457	2057	949	
P/p	639	1075	905	





Interpretation

Parameter	Malue
Fibrillation	Single
Positive sharp wave	No
Fasciculation	No
Amplitude MUPs	Normal
Duration MUPs	Significantly reduced
Polyphasy os MUPs	No
Type of interference pattern	Saturated reduced
Muscle pattern	Myogenic



Parameters MUPs

N	Take into account in the analysis	Duration, ms	Amplitude, uV	Area, nVxs	Thickness, ms	Phases	Turns	Risetime, ms	Periods per second	Peak duration, ms	Size Index
1	✓	9.46	496	788	1.59	3	3	0.775	8.1	2.68	0.979
2	✓	9.23	458	706	1.54	3	7	1.1	4.9	4.43	0.864
3	✓	9.02	689	1236	1.79	3	5	0.6	0.9	2.88	1.47
4	✓	7.32	957	445	0.465	3	5	0.3	2.0	3.93	0.427
5	✓	9.12	457	842	1.84	3	5	1.23	1.4	3.78	1.16
6	✓	7.52	1001	532	0.531	5	12	0.3		1.58	0.532
7	✓	7.65	1674	1654	0.988	3	7	0.75		5.0	1.44
11	✓	8.25	669	1059	1.58	4	8	0.65		3.13	1.23
12	✓	5.8	1022	456	0.447	4	8	0.275		1.6	0.466
13	✓	7.45	1463	2037	1.39	3	6	0.575		2.6	1.72
14	✓	7.13	842	672	0.797	3	9	0.2		2.35	0.648
16	✓	8.98	639	875	1.37	5	7	0.375		3.4	0.98
18	✓	6.65	603	566	0.94	4	10	0.35		1.65	0.5
19	✓	9.48	2057	2801	1.36	4	7	0.775		2.78	1.99
20	✓	8.07	1075	1567	1.46	5	5	1.0		3.73	1.52

Fig. 2. Myogenic remodeling of the movement unit potentials upon the needle electromyography (decreased duration, the saturated pattern). N/p — Non polyphase, P/p — Polyphase.

Molecular-genetic examination. In March 2021, blood sample was drawn for dried blood spot testing: the detected activity of the alpha-1.4-glucosidase was 0.36 μmol/l per hour (ref. ranges >2.32).

Using the method of next generation sequencing (NGS; NGS-panel), in the *GAA* gene, the pathogenic chr17:78078341T>G and chr17:78078692T>G nucleotide variants were detected in the heterozygous state. The examination was carried out at the Laboratory of Molecular Genetics and Medical Genomics of the Center for Fundamental Research in Pediatrics under the Federal State Autonomous Institution "National Medical Research Center for Children's Health", the subdivision of the Ministry of Health of the Russian Federation, the results were obtained in May 2021.

Definitive clinical diagnosis

Thus, the characteristic complaints, the anamnestic data, the data from neurological assessment, as well as the decreased activity of alpha-1.4-glucosidase in blood along with the confirmation of the presence of mutations in the *GAA* gene has allowed for stating the definitive clinical diagnosis: "Late onset Pompe disease".

Additional examination

The additional examination of the female patient was carried out at the Neurology Department of the Federal State Budgetary Scientific Institution "Scientific Center for Neurology" in June 2021, where the following results were obtained.

Laboratory tests. Alanine aminotransferase (GPT) 26 U/l, Aspartate aminotransferase (GOT) 59 U/l, Creatinphosphokinase (CPK) 516 U/l, Lactate dehydrogenase (LDH) 190 U/l, Creatinphosphokinase-MB (MB-CPK) 8 U/l (the reference ranges from the laboratory were not listed in the discharge epicrisis).

Instrumental examinations:

- echocardiography: the linear dimensions of the heart and the hemodynamic parameters in the heart valves are matching the age-specific reference ranges. The local and the global systolic function of the left ventricle is not impaired. Type I diastolic dysfunction of the left ventricle (impaired relaxation). Mitral regurgitation grade I. Tricuspid regurgitation grade I. No signs of pulmonary hypertension were detected;
- evaluation of the pulmonary functions test findings: vital capacity (VC) at the sitting position is 2.2 L (64.9% of the normal VC);
- magnetic resonance imaging (MRI) of the muscles: the data correspond to atrophy in thigh muscles with the presence of zones of swelling (stage 2b acc. to the classification by E. Mercuri, 2002).

Treatment

The enzyme replacement therapy with alpha-glucosidase medicinal product was prescribed to the patient. For two years (in 2021–2022) she was receiving Alglucosidase alfa, while the last two years (2023–2024) she was switched to Avalglucosidase alfa.

With the background of the pathogenetic therapy, the female patient subjectively reports positive dynamic changes expressed as an increase in the tolerance to physical activity along with decreasing shortness of breath.

Additional examinations conducted for dynamic follow-up at the Neurology Department of the Federal State Budgetary Scientific Institution "Scientific Center for Neurology" in August 2023, have demonstrated the following results:

1) laboratory tests: GPT 36 U/l, GOT 55 U/l, CPK 293 U/l, MB-CPK 30 U/l, LDH 162 U/l, alkaline phosphatase 189 U/l;
2) Instrumental examinations:
   - needle electromyography: the amplitude and the duration of movement unit potentials in the *musculus deltoideus* on the right side, in the *musculus biceps brachii* on the left side, in the *musculus paravertebralis* (Th12) on the left side and in the *musculus tibialis anterior* on the left side are within the normal ranges; in the *musculus biceps brachii* on the left side, there are single myogenic movement unit potentials; the amplitude of the movement unit potentials in the *musculus interosseus dorsalis* on the left side and in the *musculus vastus lateralis* on the right side is increased, the duration is within the normal ranges; other registered findings include spontaneous activity expressed as positive sharp waves in the *musculus interosseus dorsalis* and in the *musculus tibialis anterior* on the left side;
   - pulmonary functions test: VC 2.530 l (75.3% of the proper VC) at the sitting position;
   - echocardiography: signs of connective-tissue dysplasia (hypermobility of the interatrial septum, additional chordae in the left ventricle cavity); the local and the global systolic function of the left ventricle is not impaired; type I diastolic dysfunction of the left ventricle; mitral insufficiency grade I; tricuspid insufficiency grade II;

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- ultrasound examination of the abdominal cavity organs: no ultrasonographic signs of pathological changes were detected in the liver, pancreatic gland and the bile ducts.

Prognosis

Is was shown that, in adult patients with late onset Pompe disease, not receiving enzyme replacement therapy, the mortality is higher than in general population [9]. The factors, improving the prognosis and slowing the progression of the disease, include the earlier diagnostics of the disease and prescribing enzyme replacement therapy.

DISCUSSION

The patient's way to receiving the pathogenetic therapy was approximately 20 years. The long-term period of diagnostics is related to the insufficient awareness and knowledge among the neurology physicians, which were following up the patient with the diagnosis of osteochondrosis. The late onset of the disease associated with "softer" mutations in the *GAA* gene and slower progression [10] also resulted in the delaying the process of diagnostics.

The findings detected in our patient upon the physical examination, namely, the muscular weakness syndrome, had to be differentiated with a number of diseases, and first of all, the impairment level needed to be determined — myogenic, neurogenic, synaptic or central. Taking into consideration the fact that the pyramidal syndrome (increased reflexes, pathological reflexes) was not reported in a patient, the central level of impairment of the neuromuscular system was immediately rejected. Our patient also did not have the pathological muscular fatigability symptom characteristic for the synaptic level of impairment. The absence of sensitivity disorders has called into question the neurogenic level, however, the damage of the motor neuron, as well as motor neuropathies, occur without impairing the sensitivity. In differentiating the neurogenic and the myogenic levels, electroneuromyography is helpful (with a proviso that the clinically weak muscles are examined). Electroneuromyography in cases of myogenic lesions has a number of limitations related to the mosaic pattern of muscle involvement for various myopathies, as well as to the atrophy of separate muscle fibers even within a single muscle [11, 12], which is why the movement unit potentials of the muscle, in which there are no objectively signs of strength decrease, can show normal pattern, in some cases even neurogenic, which can mislead the diagnosing specialist. The distribution of muscle weakness in our case and in the majority of cases described in the literature sources for late onset Pompe disease, has a specific pattern, characteristic by the predominant damage of the axial muscles, the proximal muscles of the upper and lower limbs, with the lower limbs being affected to a greater extent with intact strength in the feet [11, 13, 14]. In this clinical case, muscle weakness prevailed exactly in thigh muscles: the weak muscles were examined (the adductor and the quadriceps), in which single spontaneous activity and myogenic remodeling of the movement unit potentials were registered. The spontaneous activity in the affected muscles indicate the on-going process of denervation as a result of dying muscle fibers, in favor of which was the detected increase of blood CPK, however, the not so high CPK level and the activity of denervation in the muscles were indicating the slow course of the pathological process, which was also shown in other cases of late onset Pompe disease [13, 15, 16].

MRI of the muscles have confirmed the morphological remodeling of the thigh muscles. The myopathic syndrome, detected clinically and confirmed instrumentally, often does not receive nosological identification and remains a syndromal diagnosis. The tracked history of muscle weakness from the school years with slow progression indicates the possible genetic genesis of myopathy; the low rising CPK level and low activity of denervation count against the inflammatory damage of the muscles (polymyositis, dermatomyositis), the characteristic features of which include very high CPK levels and the activity of denervation; while the absence of the patient's relatives in the previous generation speaks for the autosomal-recessive mode of inheritance.

The accumulation diseases are divided into two main groups: with the predominant damaging of the nervous system (leukodystrophies) and with the predominant damaging of the muscular system (glycogenoses). In our case, the leading was the damage of the muscles. The myopathic syndrome in cases of glycogenoses, the number of which counts more than ten of types, is nosologically non-specific. The mode of inheritance in the majority of glycogenoses is autosomal-recessive. In case of type I (Gierke disease), the myopathic syndrome, unlike the late onset Pompe disease, is accompanied by hyperuricemia and hypoglycemia symptoms, by chronic renal failure, having an onset of the disease at the babyhood and being characterized by delayed growth and puberty [17]; in type III (Cori disease), besides hyperuricemia and hypoglycemia, hyperlipidemia

and hypercholesterolemia are observed [17]; in case of type IV (Andersen disease), patients show delayed development and the lethal outcome occurs due the hepatic failure to the 5th year after birth [18]; type V (McArdle disease) myopathy is accompanied by muscle pain, renal failure develops with a background of myoglobinuria along with hyperuricemia [19]. Thus, the late onset Pompe disease in adults differs from other glycogenoses by the absence of delayed physical development, hypoglycemia, hyperuricemia or myoglobinuria, however, its more credible differentiation is possible based on laboratory testing of the activity of the enzymes participating in the glycogen metabolism.

CONCLUSION

The confirmation of the diagnosis of late onset Pompe disease is conducted by means of using the laboratory and genetic tests studies. Dried blood spots can be sent to the genetic laboratory by any physician from any region of the country. To provide a possibility of receiving a chance for pathogenetic therapy for a patient, the physician should not only suspect the presence of a myopathic syndrome in a patient, but he should also be aware on the possibilities of sending dried blood spot samples for testing.

Insufficient positive dynamic changes in the patient status is related to the later onset of therapy, however, the absence of subjective aggravation of the symptoms indicates the stabilization of the status and the necessity of continuing the life-time pathogenetic enzyme replacement therapy for increasing the duration of the active phase period.

ADDITIONAL INFORMATION

Supplement 1. Trendelenburg gait, the patient experiences significant difficulties when standing up from the sitting position, from the lying position, from squat on haunches, using the Gower's maneuvers (weakness of axial muscles). doi: https://doi.org/10.17816/clinpract678919-4340943

Author contributions. *A.V. Yamshchikova* — diagnostic, search and analytical work, discussion of research results, writing the article text; *T.A. Bychkovskaya* — diagnostic work, discussion of research results, editing the article text. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with face covering), in a scientific journal, including its electronic version (signed on 2025 April 12). The amount of published data is agreed with the patient.

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The Combined Approach in the Treatment of a Patient with Glaucoma and Endothelial-Epithelial Corneal Dystrophy: A Clinical Case Description

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ABSTRACT

BACKGROUND: *Penetrating keratoplasty provides a possibility of restoring vision in patients with various corneal diseases, however, just like any surgical intervention, the operation is associated with certain risks and has a number of contraindications. One of the unfavorable prognostic factors in cases of penetrating keratoplasty is uncompensated glaucoma. Penetrating keratoplasty can result in the reactive postoperative hypertension, however, this is not a standard situation. In patients with a history of glaucoma, this complication occurs much more often than in patients without previously diagnosed glaucoma. The increase of intraocular pressure during the postoperative period in patients suffering from glaucoma, can lead to the progression of the disease and to the development of the transplant disease.* ***CLINICAL CASE DESCRIPTION:*** *This article presents a clinical case of a patient with juvenile glaucoma, which underwent several glaucoma surgeries and later he received an Ex-PRESS implanted glaucoma drainage. The drainage implant was in contact with the posterior surface of the cornea, as a result of which, initially local and further total endothelial-epithelial corneal dystrophy has developed with the formation of stromal cloudiness and progressing of pain syndrome. The drainage was removed and subsequently a decision was drawn up on arranging a penetrating corneal keratoplasty, for the critical flicker fusion rate was 30 Hz, which allowed for expecting a sufficiently high vision acuity during the postoperative period. However, despite the maximal hypotensive regimen, the intraocular pressure remained high, due to which, for the purpose of decreasing it before corneal transplantation, a transscleral diode laser cyclophotocoagulation was used.* ***CONCLUSION:*** *The presented clinical case demonstrates the efficiency of transscleral diode laser cyclophotocoagulation in a patient with uncompensated glaucoma in terms of the quality of preparation to penetrating keratoplasty.*

Keywords: *clinical case; transscleral diode laser cyclophotocoagulation; refractory glaucoma; juvenile glaucoma; intraocular pressure; penetrating keratoplasty.*

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BACKGROUND

Penetrating keratoplasty is a surgical procedure, during which the whole thickness of the patient cornea is replaced with the donor material. The surgery provides a possibility of restoring vision in patients with corneal cloudiness caused by various reasons, however, just as any other surgical intervention, it is associated with certain risks and has a number of contraindications [1].

The normal level of intraocular pressure is one of the key factors affecting the transparent survival of the transplant and adequate visual rehabilitation in patients undergoing the penetrating keratoplasty, for the background of high intraocular pressure has a high risk of transplant cloudiness [1].

The elevation of intraocular pressure after the surgery can be the result of mechanical factors, such as the blockade of the angle in the anterior chamber, as well as the inflammatory and immune reactions (the activation of the inflammatory mediators can contribute to the formation of fibrous tissue and scarring in the area of the anterior chamber angle) [2].

The manifestation of reactive postoperative hypertension is a frequent complication of penetrating keratoplasty with an incidence, according to various data, ranging from 17 to 35% of the cases. Patients

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Комбинированный подход в лечении пациента с глаукомой и эндотелиально-эпителиальной дистрофией роговицы: клинический случай

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АННОТАЦИЯ

Обоснование. *Сквозная кератопластика даёт возможность восстановить зрение у пациентов с различными заболеваниями роговицы, однако, как и любое хирургическое вмешательство, операция связана с определёнными рисками и имеет ряд противопоказаний. Одним из неблагоприятных прогностических факторов при сквозной кератопластике является некомпенсированная глаукома. Сквозная кератопластика может приводить к реактивной послеоперационной гипертензии, однако это не является стандартной ситуацией. У пациентов с глаукомой в анамнезе данное осложнение встречается гораздо чаще, чем у пациентов без диагностированной ранее глаукомы. Повышение внутриглазного давления в послеоперационном периоде у пациентов, страдающих глаукомой, может приводить к прогрессированию заболевания и развитию болезни трансплантата.* ***Описание клинического случая.*** *В данной работе представлен клинический случай пациента с ювенильной глаукомой, которому были проведены несколько антиглаукомных операций и впоследствии имплантирован антиглаукомный Ex-PRESS дренаж. Дренаж контактировал с задней поверхностью роговицы, в результате чего развилась вначале локальная, а затем тотальная эндотелиально-эпителиальная дистрофия роговицы с формированием стромальных помутнений и появлением болевого синдрома. Дренаж был удалён, и впоследствии было принято решение о проведении сквозной кератопластики роговицы, поскольку критическая частота слияния мельканий составляла 30 Гц, что позволяло ожидать достаточно высокой остроты зрения в послеоперационном периоде. Однако, несмотря на максимальный гипотензивный режим, внутриглазное давление оставалось высоким, в связи с чем для его снижения перед трансплантацией роговицы была выполнена транссклеральная диод-лазерная циклофотокоагуляция.* ***Заключение.*** *Представленный клинический случай демонстрирует эффективность транссклеральной диод-лазерной циклофотокоагуляции у пациента с некомпенсированной глаукомой в качестве подготовки к проведению сквозной кератопластики.*

Ключевые слова: *клинический случай; транссклеральная диод-лазерная циклофотокоагуляция; рефрактерная глаукома; ювенильная глаукома; внутриглазное давление; сквозная кератопластика.*

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with a history of glaucoma are subject to the highest risk of increasing and stable decompensation of intraocular pressure after penetrating corneal transplantation, the control of which is especially difficult in patients at the maximum hypotensive mode, as well as among the individuals that underwent various types of surgical glaucoma interventions [3–6]. This is why the presence of past history of uncompensated glaucoma in a patient represents an unfavorable prognostic factor before the conduction of penetrating keratoplasty.

The clinical case presented demonstrates the possibility of using the transscleral diode-laser cyclophotocoagulation before the conduction of penetrating keratoplasty in patients with uncompensated or sub-compensated glaucoma at the maximum hypotensive regime. Laser cyclophotocoagulation affects the structures of the ciliary body, responsible for the production of aqueous humour. They undergo the processes of destruction, due to which, the quantity of produced humour decreases and the intraocular pressure decreases. The patient had multiple surgeries

for refractory glaucoma, due to this, the cicatrization process was initiated practically along the whole limbus, which is why it could be supposed that the success of any fistulizing surgery could be doubtful. This is why the method of surgical intervention chosen was specifically the laser cyclophotocoagulation.

CLINICAL CASE DESCRIPTION

Patient data

Patient aged 37 years, presenting on 28.04.2023 to the Department of Emergency Ophthalmology Aid of the Moscow City Ophthalmology Center under the State Budgetary Healthcare Institution "Moscow Botkin Multidisciplinary Scientific-Clinical Center" of the Healthcare Department of the City of Moscow (DEOA MCOC MBMSCC) with the complaints of pain in the left eye and low vision acuity in the left eye.

Case history. The complaints were acutely progressing from 26.04.2023. The patient was not self-medicating, presenting directly to the DEOA MCOC MBMSCC. According to oral information provided by the patient, from 2009 he was diagnosed with glaucoma in the left eye (oculus sinister, OS), for which he was constantly using Dorzolamide 2% drops twice daily, Timolol 0.5% twice daily, Proxodolol 1% + Clonidine 0.25% twice daily and Latanoprost 0.005% once daily. Past medical history of multiple (2010, 2012 and 2016) glaucoma surgeries in the ophthalmology clinical hospital. In 2016 — implantation of the Ex-PRESS drainage, followed by its removal in 2020.

On admission. The ophthalmology status of the right eye (oculus dexter, OD) shows no abnormalities: vision acuity based on visometry results of (Visus, Vis) 0.7 sph -1.0D=1.0 (where the sph means sphere and D — diopters); the intraocular pressure is 16 mm.Hg. The ophthalmology status of the left eye on admission: Vis OS=1/∞, proectio lucis certa (correct light projection, i.e. separate foci of retina have preserved the capability of reacting to light). The intraocular pressure on palpation is "++". The eyelids show no signs of abnormalities with their closure being complete, the eyelash growth pattern is correct. On palpation, the eyeball is painful. The conjunctiva and the sclera show the following: congestive injection, above the upper limbus, there is a cystically modified filtering bleb. The cornea: the surface is rough, diffuse swelling of the epithelium and stroma, cloudiness in the stroma, pronounced folds were found in the Descemet membrane. The underlying layers are covered in haze. The anterior chamber is of medium depth, the aqueous humour of the anterior chamber is transparent. The iris has intact color with smoothened pattern, at the 12 o'clock position, a basal coloboma was found. The pupil: the shape is correct, the photoreaction is weakened. The eye lens was visualized as transparent. The fundus reflex is weakened. The vitreous body, as well as the fundal structures are not available for ophthalmoscopy due to the corneal status.

Transscleral diode laser cyclophotocoagulation

Diagnosis. The patient is hospitalized to the Ophthalmology Department No. 60 of the DEOA MCOC MBMSCC according to the urgent indications with the diagnosis of: «OS: decompensated glaucoma, endothelial-epithelial corneal dystrophy. OD: mild myopia».

Medication treatment. The maximal hypotensive regimen was prescribed to the patient (with additional Brimonidin 0.15% 3 times daily; Acetazolamide 1 pill once daily for 3 days).

Surgical treatment. 29.04.2023 — the ophthalmology status of the OS shows no changes, due to which a decision was drawn up on the necessity of surgical treatment. The procedure of transscleral diode laser cyclophotocoagulation was carried out in the left eye using the infrared laser with a wavelength of 810 nm, with the power of 800 mW and with an exposure of 20 seconds; the quantity of formed coagulates is 16.

Ophthalmology status. On 30.04.2023, the patient subjectively notes positive changes. The ophthalmology status of the left eye: Vis OS=0.01 eccentric, not correctable (i.e. the vision acuity cannot be corrected with glasses).

The intraocular pressure upon palpation is "+". The eyelids show no signs of abnormalities, the eyelash growth pattern is correct. The conjunctiva is pale-pink, mild superficial injection is found along with the filtering bleb above the left limbus and with cystous changes. The surface of the cornea is rough, insignificant swelling of the epithelium, stromal cloudiness and folded Descemet membrane. The underlying structures are hazed. The anterior chamber is of medium depth, the aqueous humour of the anterior chamber is transparent. The iris pattern is smoothened, basal coloboma was found at the 12 o'clock position. The pupil has a correct shape, the photoreaction is weakened. The eye lens was visualized as transparent. The fundus reflex is weakened. The vitreous body and the structures of the fundus are not accessible for ophthalmoscopy due to the status of the cornea (Fig. 1).

Recommendations on discharge. On 03.05.2023, the patient was discharged with the recommendations

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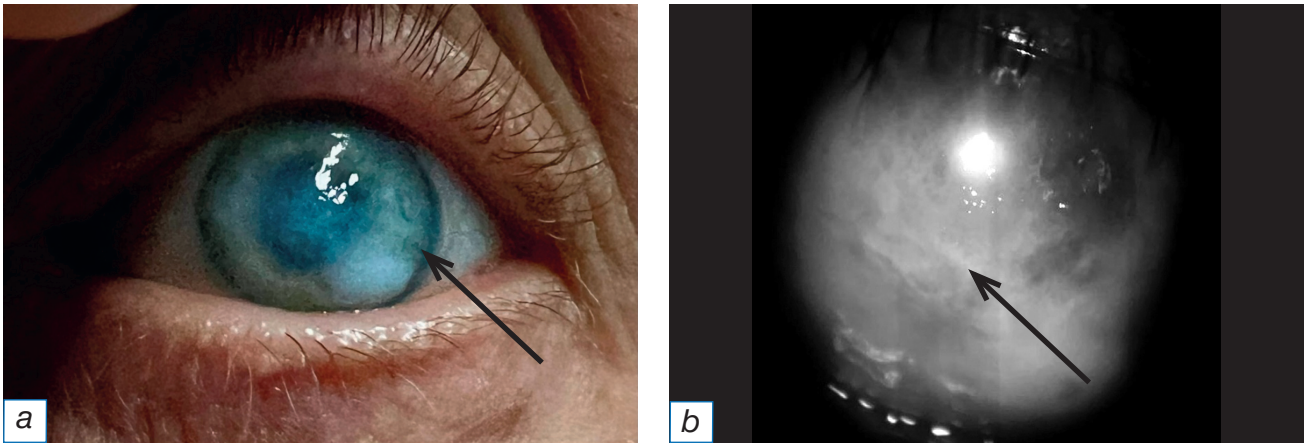

Fig. 1. Status of the eye after laser cyclophotocoagulation (before the conduction of the penetrating keratoplasty): *a* — appearance ×3; *b* — appearance ×16. The arrow indicates the swelling of the cornea with cloudiness in the stroma).

of following the hypotensive mode: Dorzolamide 2% twice daily, Timolol 0.5% once daily, Brimonidin 0.15% 3 times daily, Proxodolol 1% + Clonidine 0.25% twice daily, Latanoprost 0.005% once daily. Additional prescriptions included the anti-inflammatory, the antibacterial and the epithelization therapy: Bromfenac 0.09% eye drops once daily, Ciprofloxacin 0.3% + Dexamethasone 0.1% eye drops 3 times daily, Dexpanthenol 5% gel 3 times daily, intramuscular administrations of Ketorolak 30 mg once daily.

21.07.2023 — ophthalmology status (OS): VisOS=0.01, not correctable. Intraocular pressure — 15 mm.Hg. Critical flicker fusion rate — 30 Hz. The general eye status is stable. The conjunctiva is pale-pink, no signs of discharge were found. The status of the anterior and posterior segments of the eyeball corresponds to the ophthalmology status of 30.04.2023.

Penetrating keratoplasty

Diagnosis. OS: endothelial-epithelial corneal dystrophy, repeatedly operated juvenile grade IIIA glaucoma. OD: mild myopia.

Surgical treatment. On 01.11.2023, the patient was again hospitalized to the Ophthalmology Department No. 60 of the DEOA MCOC MBMSCC.

Surgery was conducted in the left eye: penetrating keratoplasty (diameter of the transplant — 8.5 mm, fixation with interrupted sutures).

Medication treatment. At the In-Patient Department, anti-inflammatory, antibacterial and epithelization therapy was prescribed: Bromfenac 0.09% drops once daily, Ciprofloxacin 0.3%+ Dexamethasone 0.1% drops 3 times daily, Phenylephrine 5.0% drops + Tropicamide 0.8% 3 times daily, Dexpanthenol 5% gel 3 times daily, intramuscular Ketorolak at a dosage of 30 mg once daily, intravenous Dexamethasone at a dosage of 8 mg once daily, oral Omeprazol — 20 mg once daily.

Ophthalmology status. Upon the examination on 02.11.2023, the patient has no complaints, subjectively reporting the improvement of the status. Ophthalmology status of the left eye: Vis OS=0.05, not correctable. Intraocular pressure 17 mm.Hg. The eyelids are unremarkable, capable of complete shutting, the eyelash growth pattern is correct. On palpation, the eyeball is painless. The conjunctiva and the sclera are pale-pink, above the upper limbus, there is a cystically changed filtering bleb. The cornea status is the following: the surface is smooth, glossy, the penetrating transplant is transparent, adapted, the interrupted sutures are clean and competent, single folds were found in the Descemet membrane. The anterior chamber is of medium depth, the aqueous humour of the anterior chamber is transparent. The iris has no changes in its color, the pattern is smoothened, at the 12 o'clock position, a basal coloboma was detected. The pupil: the shape is correct, active photoreaction is present. The eye lens is transparent. The fundus reflex is pink. The vitreous body contains floating cloudiness. The ocular fundus: the optic nerve disc is pale with a gray shade, the margins are clear, excavation 0.9, the vascular bundle is dislocated towards the nose, the macular area and the peripheral area show no signs of gross changes (Fig. 2).

Recommendations on discharge. On 03.11.2023, the patient was discharged for further dynamic follow-up by the ophthalmologist at the place of residence. The hypotensive regimen was corrected, the prescriptions included Dorzolamide 2% + Timolol 0.5% twice daily, Proxodolol 1% + Clonidine 0.25% twice daily. Additional prescriptions: Bromfenac 0.09% eye drops

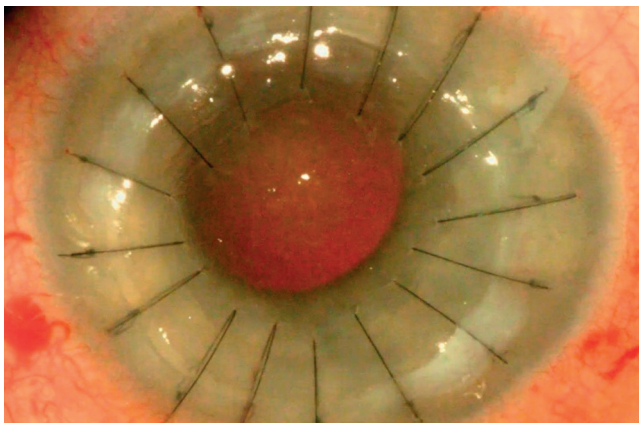

Fig. 2. Status of the eye after penetrating keratoplasty: postoperative day 1.

once daily, Phenylephrine 5.0% + Tropicamide 0.8% eye drops 3 times daily, Dexpanthenol 5% gel 3 times daily, Ciprofloxacin 0.3% + Dexamethasone 0.1% eye drops 3 times daily.

Outcome and results of further follow-up

On 22.01.2024, the patient had no complaints, the general status was satisfactory. Ophthalmology status of the left eye: Vis OS=0.16 with a 1.5 mm diaphragm, not correctable. Intraocular pressure — 17 mm.Hg. The eyelids show no signs of abnormalities, the eyelash growth pattern is correct. The conjunctiva is pale-pink, the filtering bleb was detected under the upper limbus, cystous changes were also found. The surface of the cornea is smooth and glossy, the penetrating transplant is transparent, adapted, and the interrupted sutures are clean and competent. The anterior chamber is of medium depth, the aqueous humour of the anterior chamber is transparent. The iris pattern is smoothened, the basal coloboma was found at the 12 o'clock position. The pupil has a correct shape, active photoreaction is present. The eye lens is transparent. The fundus reflex is pink. The vitreous body contains floating cloudiness. The ocular fundus: the optic nerve disc is pale with a gray shade, with clear margins, showing an excavation of 0.9, the vascular bundle is dislocated towards the nose, the macular area and the periphery show no signs of gross changes (Fig. 3).

At the moment of compiling the clinical case (May of 2024), Vis OS=0.2 with a diaphragm of 1.5 mm, not correctable. The intraocular pressure is 16 mm.Hg. The eye status is stable, no signs of discharge were found. The transplant is transparent, adapted, the sutures are clean and competent. The status of the anterior and posterior segments of the eye corresponds to the ophthalmology status of 22.01.2024.

Prognosis

As a result of conducted treatment (transscleral diode laser cyclophotocoagulation with further penetrating corneal transplantation) and dynamic follow-up within one year, the patient was diagnosed with an improvement of the vision acuity with correct light projection of up to 0.2 with a critical flicker fusion frequency of 30 Hz, which allows for supposing the favorable prognosis in terms of further improvement of the visual functions.

DISCUSSION

Uninterrupted transscleral diode laser cyclophotocoagulation is an effective method of stabilizing the ophthalmotonus in cases of insufficiency of surgical treatment in patients with refractory glaucoma [3, 4]. This type of surgical intervention, despite the high risk of developing complications (hemorrhagic, hypotension, cataracts, subatrophies of the eyeball), shows higher hypotensive effect comparing to the micro-impulse transscleral diode laser cyclophotocoagulation, which is why it is the method of choice in cases of repeatedly operated refractory glaucoma [7].

For the transparent survival of the keratotransplant, the normalization of the intraocular pressure is necessary [8]. An additional factor of corneal transplant survival is the absence of burn-induced reaction. Due to the fact that the applications of uninterrupted transscleral diode laser cyclophotocoagulation were

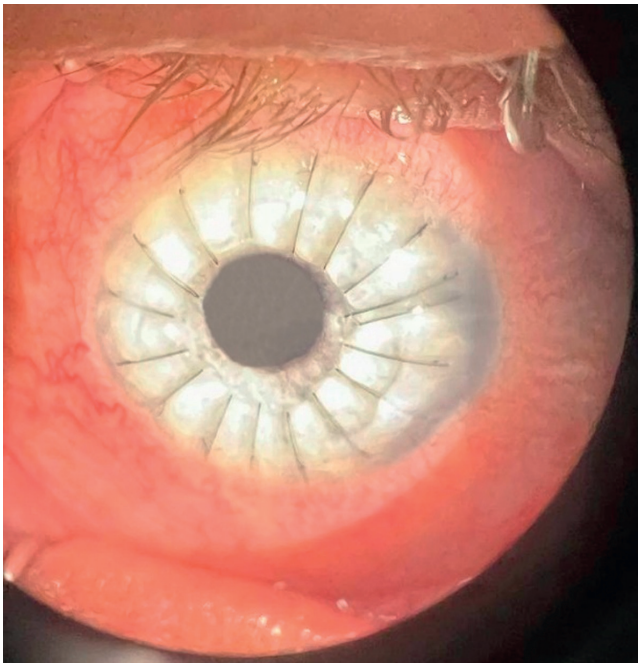

Fig. 3. Status of the eye after penetrating keratoplasty: follow-up month 3.

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applied distantly from the limbus zone, it can be judged that there was no significant damage of the cell growth zone, affecting further survival of the keratotransplant [9]. Within this context, there was no massive immune response observed, which provides adequate survival of the keratotransplant [10].

Taking into consideration all of the above, it can be supposed that transscleral diode laser cyclophotocoagulation can be carried out for decreasing the intraocular pressure in cases of repeatedly operated refractory glaucoma before the conduction of penetrating keratoplasty without the increased risk of developing the transplant disease [1].

As of today, the published clinical cases of such kind are few, however, the ones available demonstrate that transscleral diode laser cyclophotocoagulation allows for preserving the achieved vision acuity, the degree of keratotransplant transparency and for minimizing the required intake of hypotensive medications (duration of follow-up — up to 2 years) [3, 5].

CONCLUSION

This clinical case demonstrates the efficiency of using transscleral diode laser cyclophotocoagulation in a patient with uncompensated glaucoma as a preparation phase for conducting the penetrating keratoplasty. However, a single case is not enough to make convincing conclusion on high efficiency of this procedure in this category of patients, which, indeed, requires the conduction of additional research.

ADDITIONAL INFORMATION

Author contributions. *L.A. Popova:* study design development, review of publications on the topic of the article, manuscript writing; *A.I. Ibraimov:* patient treatment, approval of the concept and design of the study, manuscript writing; *I.B. Alekseev:* patient treatment, approval of the concept and design of the study, editing; *G.Sh. Arzhimatova*: manuscript editing. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication. The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2024 November 14). The volume of published data was agreed upon with the patient.

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Implantation of an Additional Intraocular Lens for Keratoconus in a Pseudophakic Eye

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ABSTRACT

BACKGROUND: *In the accessible literature sources, there is insufficient information on the correction of refraction abnormalities in cases of keratoconus, due to which exploring the modern approaches in the implantation of additional intraocular lenses, including the choice of indications, the surgical technique and the post-operative follow-up, gains major importance for managing the patients with this disease.* ***CLINICAL CASE DESCRIPTION:*** *The patient G., aged 42 years, presented with the complaints of decreased visual acuity in the left eye. Past medical history of progressing decreased visual acuity in both eyes from 2018, the diagnosis set was the following: "Right eye (OD): keratoconus stage I, left eye (OS): keratoconus stage II". In 2018, the implantation of intrastromal corneal ring segments in both eyes was conducted, in 2019 — refractive lensectomy with the implantation of the AcrySof IQ Toric SN6AT8 intraocular lens (Alcon, USA) in both eyes. The examination results in the OS upon presenting were the following: non-corrected visual acuity 0.05, maximum corrected visual acuity 0.5; autorefractometry: sph +2.25 D; cyl -9.50 D ax 81°; intraocular pressure — 17 mm.Hg. For correcting the refractive error that is preventing from achieving the high visual acuity (far vision), the implantation of additional intraocular lenses was carried out (Sulcofix Toric Care group, India). The results of examining the OS during the first 24 hours after surgery were the following: non-corrected visual acuity of the OS 0.8; autorefractometry: sph -0.25 D; cyl -14.50 D ax 81°; intraocular pressure — 17 mm.Hg.* ***CONCLUSION:*** *The implantation of additional Sulcofix Toric intraocular lenses have demonstrated its efficiency in correcting the refractive error in the pseudophakic eye with keratoconus, however, due to the irregular astigmatism characteristic for keratoconus, the residual defect can still persist.*

Keywords: *additional intraocular lenses; IOL; pseudophakia; keratoconus; residual ametropia; additional correction; clinical case.*

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List of abbreviations

IOL — intraocular lens
MCVA — maximum corrected visual acuity
NCVS — non-corrected visual acuity
Ax (axis) — the axis of the cylinder measured in degrees (from 0 to 180)
Cornea back — posterior surface of the cornea
Cornea front — anterior surface of the cornea
Cyl (cylinder) — optical power of the cylinder
K1 and K2 — keratometry values in the anterior part of the cornea: K1 — flat, K2 — steep
OD (oculus dexter) — right eye
OS (oculus sinister) — left eye
Sph (sphere) — value of the optic power of the lens, expressed in diopters (dioptria, D)

BACKGROUND

The topicality of the research devoted to the implantation of the additional intraocular lens (aIOL) for keratoconus is resulting from several key factors. First of all, keratoconus represents a progressing dystrophic disease of the cornea, which is characterized by its thinning and bulging into the central and/or the paracentral areas, which leads to the development of irregular astigmatism, decreased visual acuity and significant aggravation of the quality of life among the patients [1].

Имплантация добавочной интраокулярной линзы при кератоконусе на артифакичном глазу

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АННОТАЦИЯ

Обоснование. *В доступных источниках литературы недостаточно информации по коррекции аномалий рефракции при кератоконусе, в связи с чем изучение современных подходов к имплантации добавочных интраокулярных линз, включая выбор показаний, технику операции и постоперационное наблюдение, имеет важное значение.* ***Описание клинического случая.*** *Пациент Г., 42 года, обратился с жалобами на снижение зрения на левом глазу. В анамнезе с 2018 года прогрессирующее снижение остроты зрения на оба глаза, выставлен диагноз: «Правый глаз (OD): кератоконус I стадии, левый глаз (OS): кератоконус II стадии». В 2018 году проведена имплантация интрастромальных роговичных сегментов на оба глаза, в 2019 году — рефракционная ленсэктомия с имплантацией интраокулярной линзы на оба глаза. Результаты обследования OS при обращении: некорригированная острота зрения 0,05, максимально корригированная острота зрения 0,5; авторефрактометрия: sph +2,25 D; cyl -9,50 D ax 81°; внутриглазное давление 17 мм рт.ст. Для коррекции аномалии рефракции, препятствующей достижению высокой остроты зрения вдаль, выполнена имплантация добавочных интраокулярных линз. Результаты обследования OS в первые сутки после операции: некорригированная острота зрения OS 0,8; авторефрактометрия: sph -0,25 D; cyl -14,50 D ax 81°; внутриглазное давление 17 мм рт.ст.* ***Заключение.*** *Имплантация добавочных интраокулярных линз продемонстрировала свою эффективность в коррекции аномалии рефракции на артифакичном глазу с кератоконусом, однако из-за нерегулярного астигматизма, характерного для кератоконуса, остаточный дефект всё же может сохраняться.*

Ключевые слова: *добавочные интраокулярные линзы; ИОЛ; артифакия; кератоконус; остаточная аметропия; докоррекция; клинический случай.*

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The occurrence rates of keratoconus in European population ranges from 5 to 23 cases per 100 000 residents with the mean worldwide rate of 54 per 100 000 [2]. The disease affects the representatives of all the ethnicities and both genders. Usually, the symptoms of keratoconus start to manifest in the adolescence years. Higher rate of occurrence is observed among the Asian-looking individuals [3]. The early research has revealed that the disease is more commonly observed in women — 52.9% as compared to 47.1% in men [2]. During the last two decades, a growth is reported in the number of registered cases, which can be explained by the improvement of diagnostic methods and by the increased detectability of the early disease stages.

Traditional methods of optic correction for keratoconus, such as glasses and contact lenses, often become ineffective at the later stages of the disease. The progressing irregular astigmatism results in the discomfort, the intolerability of lenses and unstable refraction. The surgical treatment methods [4, 5], including the corneal crosslinking, the implantation of intrastromal corneal ring segments and various keratoplasty variants, do not always provide sufficient correction of ametropy [6–8].

Taking into consideration that the percentage of young men among the keratoconus patients is sufficiently high, special topicality gains the achieving the good visual function and preserving the vision quality in the long-term perspective. The implantation of aIOL in the settings of correct selection of the optic power and thorough assessment of the status of the cornea, of the depth of the anterior chamber and of the

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keratoconus progression level can significantly improve the quality of life for the patients, with improving their social adaptation and professional relevance. For the success of such surgeries, it is necessary to follow the specific criteria, in particular, the stability of keratoconus within not less than a year along with the presence of transparent cornea at the optic zone [7].

In the accessible literature sources, there is insufficient information on the correction of refraction abnormalities in cases of keratoconus, due to which exploring the modern approaches in the implantation of aIOL, including the choice of indications, the surgical technique and the post-operative follow-up, gains major importance for managing the patients [9–11]. The analysis of clinical results after such interventions allows for evaluating their clinical efficiency, as well as for defining the remote consequences for patients [12, 13].

In this article, describing the clinical case, an assessment was carried out of the efficiency of intraocular correction of ametropy using the implantation of an additional intraocular lens in a patient with pseudophakia and grade I–II keratoconus.

CLINICAL CASE DESCRIPTION

Patient information

Patient G., aged 42 years, presented to the Orenburg affiliated branch of the Federal State Autonomous Institution «NMRC «Interdisciplinary Scientific and Technical Complex “Eye Microsurgery” named after the academician S.N. Fedorov» under the Ministry of Health of the Russian Federation with the complaints of decreased visual acuity in the left eye.

Disease history. From 2018, the patient reports the progressing decrease of visual acuity in both eyes, especially in the left one. The patient was diagnosed with the following diseases: “OD — keratoconus stage I, OS — keratoconus stage II”. In 2018, implantation of the intrastromal corneal ring segments was done in both eyes. For the purpose of improving the visual acuity, according to the will of the patient, in 2019 he underwent a lensectomy (refractive replacement of the eye lens) with an implantation of the intraocular lens (IOL) in both eyes, however, due to the past history of operated keratoconus, the target refraction was not achieved. The surgery was done using the standard method of ultrasonic phacoemulsification of the cataract with the implantation of IOL by means of the EVA surgical system (DORC, The Netherlands). The implanted intraocular lens was the AcrySof IQ Toric SN6AT8 +20.0 (Alcon, USA).

The non-corrected visual acuity (NCVA) before surgical intervention in the left eye was 0.05, maximum corrected visual acuity (MCVA) — 0.2.

Autorefractometry: sph +4.5, cyl -10.25, ax 80°. Intraocular pressure — 13 mm.Hg.

NCVA after surgery in the left eye was 0.05, MCVA — 0.5.

Autorefractometry: OS — sph +1.5; cyl -9.5 ax 86°. Intraocular pressure — 17 mm.Hg.

laboratory and instrumental diagnostics

The patient underwent a standard ophthalmology examination, including the pre- and postoperative visometry, namely the following: NCVA and MCVA, refractometry, ophthalmometry, perimetry, keratopachymetry, tonometry, biomicroscopy, gonioscopy, ophthalmoscopy, endothelial microscopy, optic biometry and corneal topography. The measurements of NCVA and MCVA were carried out using the CV-3000 phoropter with ACP5 chart panel manufactured by Topcon (Japan). The analysis of the anterior and the posterior elevation of the cornea, as well as the measurements of corneal thickness and the depth of the anterior chamber (ACD) were conducted using the Scheimpflug-topography device from Pentacam (Germany). The endothelial microscopy was performed using the TOMEY EM-3000 contacted and non-contacted endothelial microscope (Tomey, Japan), while the optical coherent tomography was done by means of using the Optovue SOLIX device (Optovue, USA).

NCVA — 0.05; MCVA — 0.5. Autorefractometry results: OS (sph +2.25 D; cyl -9.50 D ax 81°); intraocular pressure 17 mm.Hg.

Provisional diagnosis

Bases on the examination results, the diagnosis set was the following: “H16.8 OS Keratoconus. Status post implantation of the intrastromal corneal ring segments. Induced mixed astigmatism. Pseudophakia. Amblyopia of medium degree of severity. H16.8 OD Keratoconus. Status post implantation of the intrastromal corneal ring segments. Induced mixed astigmatism. Pseudophakia”.

Treatment

In order to correct the refractive error preventing from achieving the high visual acuity (far vision), an implantation of the aIOL Sulcofix Toric was carried out (sph — 3.0 D, cyl +6.0 D) (Care Group, India).

The surgical access was gained by means of the main corneal tunnel incision with a diameter of 2.2 mm at the 3 o'clock position and via the two auxiliary corneal incisions with a diameter of 1.2 mm at the 1 and 7 o'clock positions. The anterior chamber was refilled with viscoelastic media — the 2% solution of hypromellose (Appavisc, India). The completion of surgery included the bimanual removal of the remaining viscoelastic gel and the hydration of the corneal incisions. The surgery was conducted using the EVA surgical system (DORC, The Netherlands).

Follow-up and outcomes

The assessment and examination conducted during the first 24 hours after surgery, have demonstrated the transparent smooth cornea, the presence of intrastromal corneal ring segments, the hermetically sealed corneal incisions, the deep anterior chamber, the unremarkable iris, as well as the correct position of the aIOL and of the posterior chamber IOL. The vitreous body and the ocular fundus show no signs of abnormalities. NCVA OS 0.8 n.c.

Autorefractometry results: OS (sph -0.25 D; cyl -14.50 D ax 81°). Intraocular pressure — 17 mm.Hg.

Keratometry findings (Pentacam, Germany) OS. Cornea front (anterior surface of the cornea): K1 36.4 D, ax 82°; K2 46.6 D, ax 172°. Astigmatism (Astig.) 10.2 D. Cornea back (posterior surface of the cornea): K1 - 5.3 D; K2 - 6.6 D. Astig. 1.3 D (Fig. 1).

One month after surgery, the assessment and examination show that the cornea is transparent and smooth; the intrastromal corneal ring segments were clearly detected, the corneal incisions are sealed, the anterior chamber is deep, the iris is unremarkable, the aIOL is correctly positioned, just like the IOL in the posterior chamber. The vitreous body and the ocular fundus show no signs of abnormalities (Fig. 2).

NCVA in the OS was 0.5, MCVA in the OS — 0.5 cyl -2.0 D ax 100° = 0.7.

Autorefractometry results. OS: sph -0.25 D; cyl -2.0 D ax 100°. Intraocular pressure — 19 mm.Hg.

Keratometry findings (Pentacam, Germany) OS. Cornea front: K1 38.6 D, ax 87°; K2 45.1 D, ax 177°. Astig. 6.5 D. Cornea back: K1 -5.5 D; K2 -6.4 D. Astig. 0.8 D (Fig. 3).

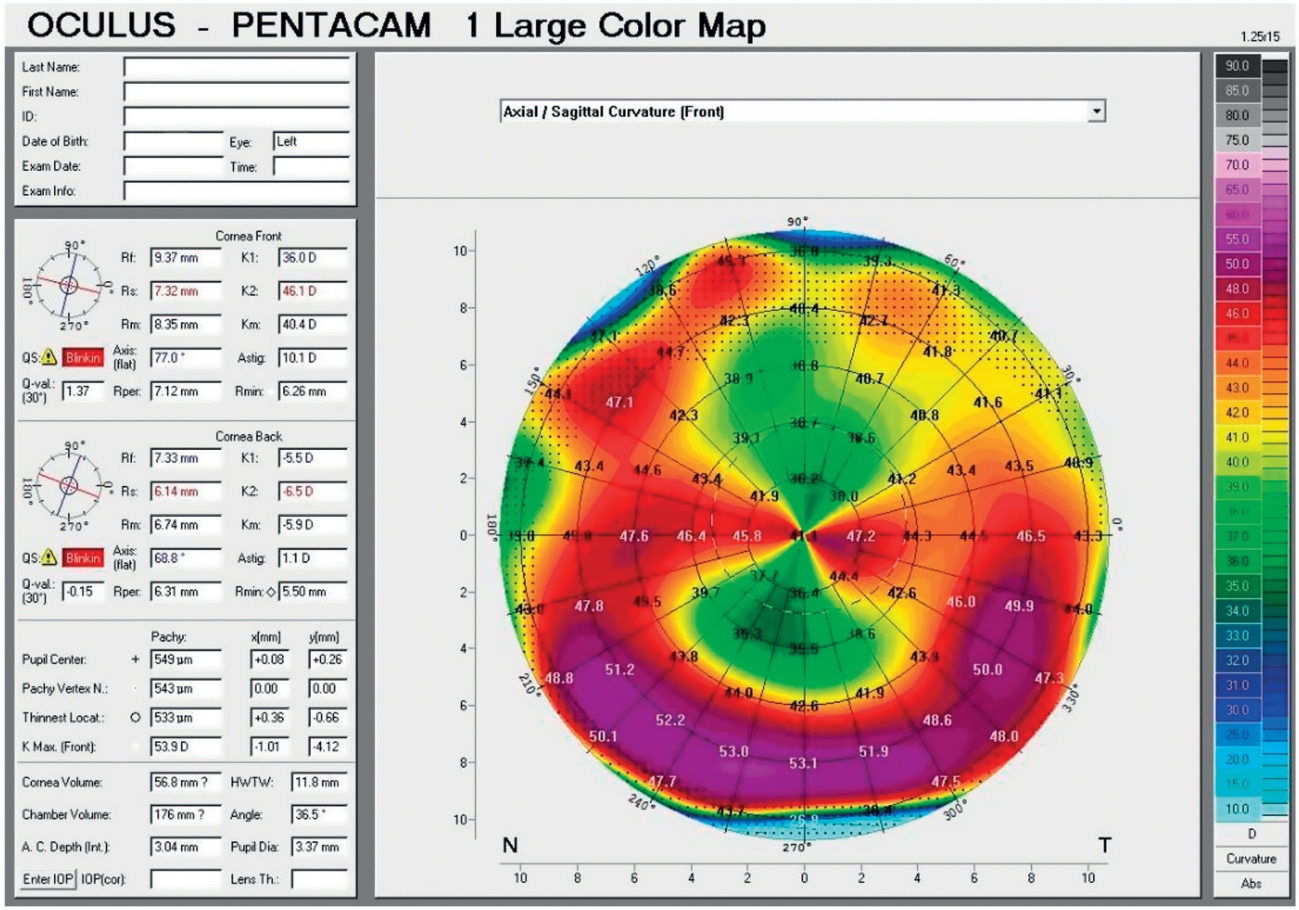

Fig. 1. Keratotopography image of the left eye before surgical intervention.

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Definitive diagnosis

The following clinical diagnosis was set to the patient: "H16.8 OS Keratoconus. Status post implantation of the intrastromal corneal ring segments. Induced mixed astigmatism. Pseudophakia. Amblyopia of medium degree of severity. H16.8 OD Keratoconus. Status post implantation of the intrastromal corneal ring segments. Induced mixed astigmatism. Pseudophakia".

Prognosis

The achieved results indicate the favorable outcome: preserved transparency of the optical media, physiological values of intraocular pressure (17–19 mm.Hg.), as well as stable refraction, allowing to consider the combined approach with the using toral aIOL an effective solution for correcting the severe astigmatism in patients with keratoconus after previous surgical interventions. Such a combination of methods increases the chances of stabilizing the visual functions and of improving the quality of life.

Despite the positive effect, taking into consideration the potential progression of keratoconus, regular topography and clinical monitoring is necessary, especially in the relatively early post-surgery period.

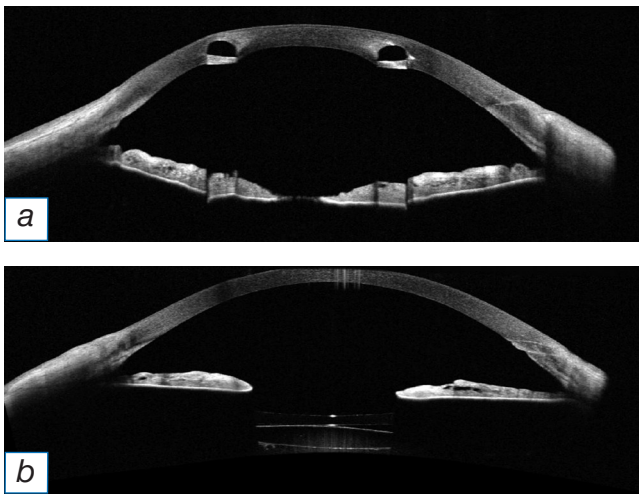

Fig. 2. Optical coherent tomography of the left eye after surgical intervention: *a* — intrastromal corneal ring segment; *b* — the posterior chamber shows the presence of an additional intraocular lens and of the posterior chamber intraocular lens.

DISCUSSION

The results obtained during the present research indicate that the implantation of aIOL can be effectively and safely used in adult patients. In the research works

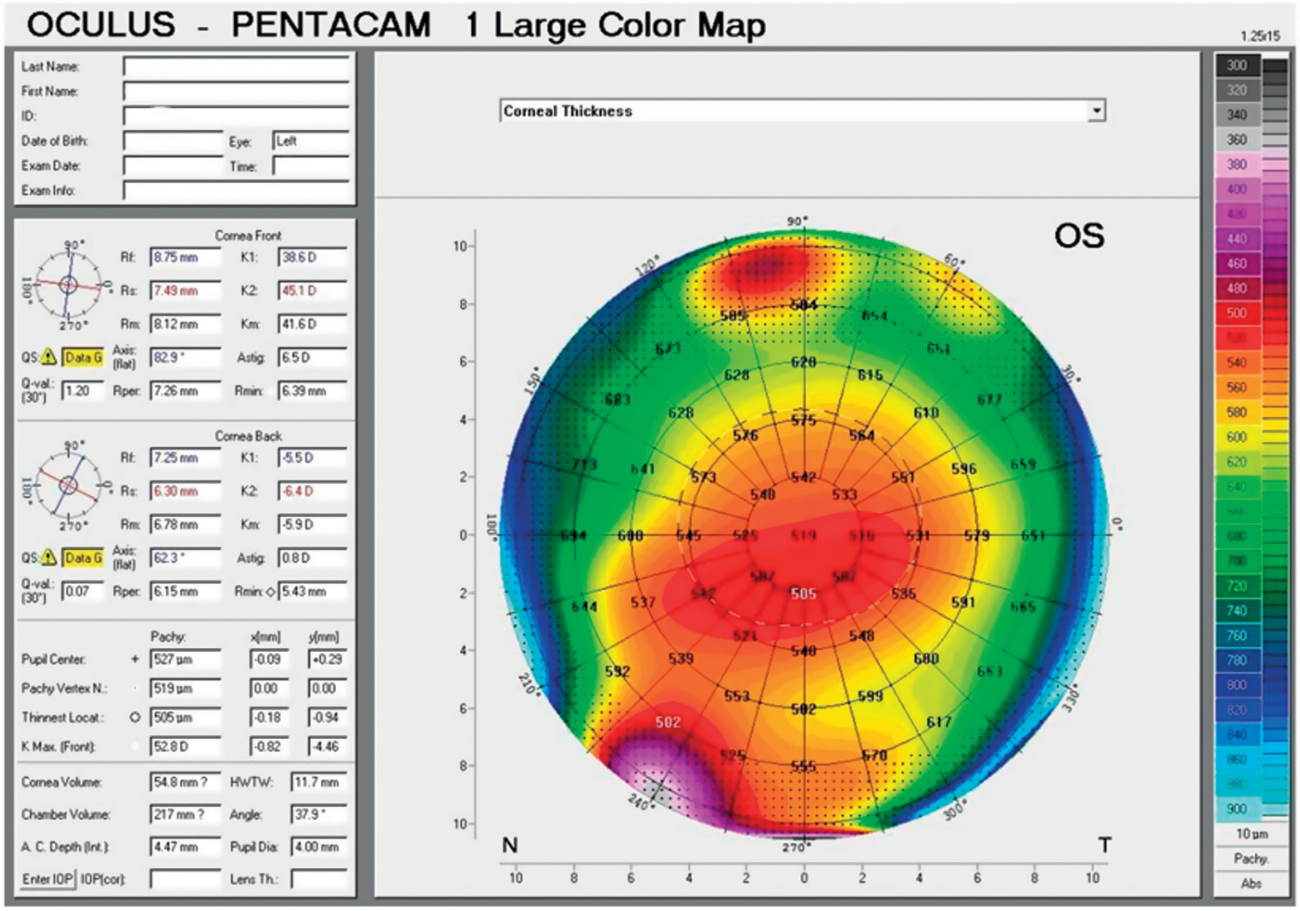

Fig. 3. Keratotopography image of the left eye after surgical intervention.

arranged in our country, the implantation of aIOL is also possible in children. Despite the fact that the demonstrated technology has still not gained wide spreading in our country, the data on the insignificant loss of endothelial cells (not more than 3%), as well as on preserving the intraocular pressure and outflow facility values within the normal ranges in patients after surgery are promising [11].

From the point of view of refractive efficiency, additional implantation of non-spherical or toric IOL allows for achieving the stable optical result for a short time, which meets the modern requirements for cataract surgery and for refractive procedures. The high accuracy of calculations and the ease of performing the surgery, as well as the specific features of the lens structure, provide its stable fixation in the iridociliary sulcus, which eventually provides the stability of the refractive effect and the absence of interactions between the surfaces of the main and the additional IOL. Such parameters are important both for the patients with ametropy after the phacoemulsification of the cataract and for the children with congenital abnormalities of the eye lens, requiring the correction of refraction [11, 14].

Thus, the results of the present research together with the literature data show the perspectivity of using the aIOL for correcting ametropy and increasing the vision quality after cataract phacoemulsification, nevertheless, further accumulation of clinical experience and arranging additional comparative research is necessary with longer follow-up period and more extensive patient samples. This shall allow for better evaluation of the remote refraction stability, the possible changes in the topography of the anterior ocular segment, as well as to compare the efficiency of various aIOL models in various clinical settings.

CONCLUSION

The implantation of the Sulcofix Toric aIOL have demonstrated its efficiency in correcting the refractive abnormalities in the pseudophakic eye with keratoconus, however, due to the irregular astigmatism, characteristic for keratoconus, the residual defect can still persist. The substantial clinical effect is demonstrated by the combined approach to the treatment of keratoconus, with this, the patient requires regular topography and clinical control for the timely detection of possible disease progression.

ADDITIONAL INFORMATION

Author contributions. *A.D. Chuprov:* concept and design of the study, *V.L. Kim:* surgical treatment and examination of the patient; *I.A. Stolyar:* processing of the study results, writing the text of the article. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (date of signing: 22.01.2025). The volume of published data was agreed upon with the patient.

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