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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

SURGICAL STRATEGY FOR LARGE EXTRACEREBRAL SUBTENTORIAL TUMORS

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Extracerebral subtentorial tumors make up to 20% of all intracranial neoplasms. The most common among them are vestibular schwannomas and meningiomas [6].

Many patients seek a nurosurgery at the stage when the tumors are large (larger than 3 cm in diameter) and this is in spite of morden methods of neuroimaging [7]. Uppon admision the patients condition quiet complicated difficul partly due tumor size, partly due CSF blockage [10].

Under these conditions, radical surgery over large subtentorial tumors is associated with a high risk of postoperative complications [13]. Despite siagnificant development of imaging technology, intraoperative monitoring, and microsurgical treatment, problems one of tottal and safe large subtentorial tumors removal remain unsolved. The most critical problem relating to large tumors of this localization is postoperative edema [5,15]. Also brainstem ischemic stroke is not rare and this would partly due to the tumors overgrowthing the vertebral and basilar arteries [9].

Material and methods. Retrospective analysis of 59 patients with large (more than 3 cm) tumors to the posterior cranial fossa operated over 2015-2019 yy.

Tumors localization: Most of the cases presented with subtentorial meningioma patients - 23 cases (39% of the total).

Petroclival meningiomas were most observed among of them in 13 cases (22% of the total); Foramen magnum meningiomas occurred in 5 patients (8.5% of the total), the same number of patients had tentorium meningiomas - 5 patients (8.5%); The second group, by the number of observations, were patients with vestibular schwannomas - 22 (37.2% of the total group with large subtentorial tumor patients). Clival chordomas were observed in 6 cases (10.2% of the total). Posterior fossa cholesteatomas - 3 patients (5.1%); foramen jugular schwannomas (3 patients) were uncommon and occurred in only 5.1% of the total number of patients with large posterior fossa tumors. The smallest number of patients occurred with large paragangliomas and was 3.4% (2 cases) of the total.

Tumor size was important in managin of the patients and planning the surgical strategy. *The average size tumors.* Average size of vestibular schwannomas were 3.3 cm (with a maximum size of 5.5 cm). Petroclival meningiomas was on average 3.1 cm in diameter (with a maximum size of 4.9 cm). At the same time the foramen magnum meningiomas were slightly smaller, their average size were 3.2 cm and the maximum size was 3.9 cm. Tentorium meningiomas were the largest in their histological group and reached on average 3.6 cm, with the maximum size of 5.2 cm. Even larger in size there were the clival chordomas with the posterior cranial fossa spread. Their average size reached 4.5 cm, with the maximum size as high as 7.8 cm. The average size of the foramen jugular schwannomas were 3.1 cm, and the maximum were 5.0 cm. The maximum size of the paragangliomas were 3.9 cm, the average were 3.3 cm. Posterior cranial fossa cholesteatomas - 3.3 cm (maximum - 4.5 cm).

Results and discussion. Large benign extracerebral tumors have slow growth and long time stay asymptomatic. This leads to brain stem compression and excessive tumor vascularization. The main point of the surgery is the safely while maintaining radicality tumor removal. For example, the number of neurological complications in patients with petroclival meningiomas can reach up to 41%, while their quality of life postoperatively decrease from 80 to 70 points by Karnofski scale [12].

The combination of approaches make it possible to decreases at the very early stage the intracranial pressure [3]. This would give a possibility to perform tumor dissection, critical vascular structures dissection on the relax brain decrease intracranial pressure. Having riched decrease in intracranial brain pressure, thus decreasing at the early clean operative field makes it remarkably decrease complications while doing dissection especially brain sterm, critical vascular and nerve dissection. Tumor debulking at the first stage using different surgical approaches thus achieving subtentorial decompression make it possible to early visualize vertebrobasilar arteries with their branches. Whit this in mind preventing any injury to them.

Also combination of approaches at a time over giant subtentorial tumors removal prevents and decreases the risk of postoperative complications such as meningitis (no intraoperative trauma to the cerebellum), strokes (subtentorial vessles clearly seen at the tumor early debulking) [11]. Surgery strage depending relating to tumor location **(**Table 1**).**

Table 1. Surgical approaches to large subtentorial tumors

Surgical approach	Number of operations	Pathology
Suboccipital retrosigmoid approach 37 (in combination with presigmoid approach 4)	37 4	Vestibular schwannomas (22) Petroclival meningiomas (8) Tentorium meningiomas (5) Posterior cranial fossa cholesteatomas (3) Paragangliomas (2) Foramen magnum meningiomas (1)
Endoscopic endonasal transclival approach	9	Petroclival meningiomas (5) Clival chordomas (4)
Endoscopic transoral transclival approach	2	Clival chordomas (2)
Far lateral approach	7	Foramen magnum meningiomas (4) Foramen jugular schwannomas (3)

Suboccipital retrosigmoid approach – 37 cases (in combination with presigmoid approach – 4 cases). Considering that posterior cranial fossa tumors can reach large size thus causing intracranial pressure. Retrosigmoid approach used along may cause trauma to the cerebellum and brain sterm [4]. Tractions applied to the cerebellum during access to the tumor may be damaging cerebellum, which is manifested in postoperative edema or even intracerebellum hemorrhage. To avoid this in 4 cases (where was especially large subtentorial tumors) we did presigmoid approach to debulking tumor. Presigmoid approach would give us direct exposure of a large petroclival tumor or vestibular schwannoma immediate debulking does achiving decompression and decrease a subtentorial pressure. We would further procced it retrosigmoid approach at the one would give better tumor dissection especially this dissection would ready be done on relaxed cerebellum. This is particularly important for petroclival meningioma, their consistency expect to be solid. (Fig. 1).

For less solid tumors (like vestibular schwannomas) it may be used retrosigmoid approach along expectine tumor is sucktible at very early stage. Still in tumor debulking is on the top of the page as it is only decreasing intracranial subtentorial pressure may give posibility to perfom save tumor dissection (expecial critical structures and brain stem (Fig. 2).

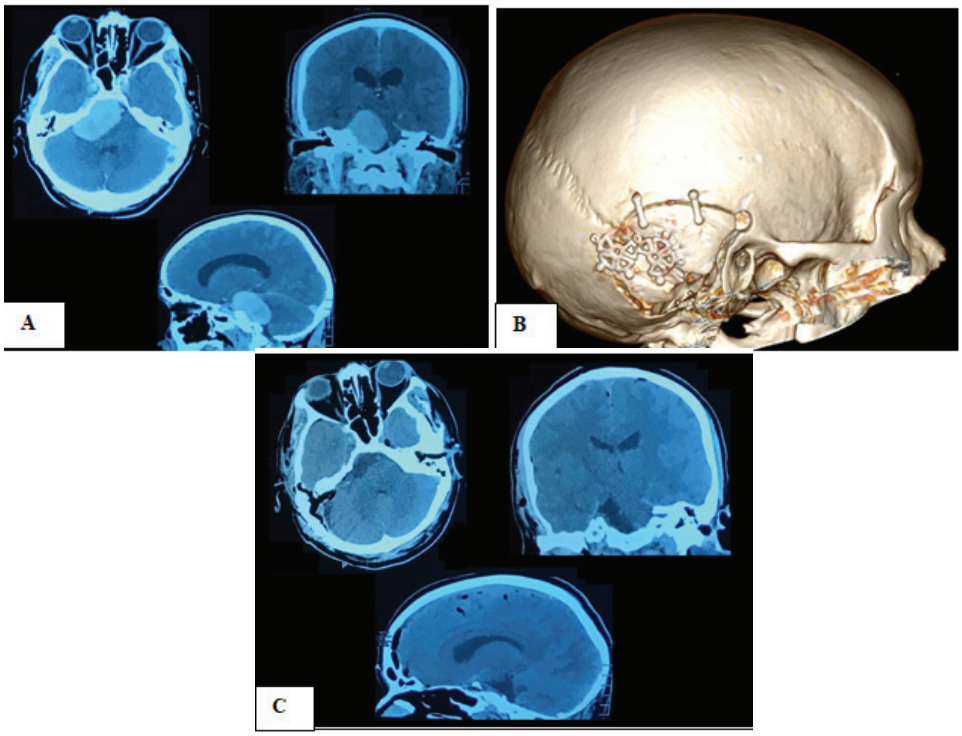

Fig. 1. Petroclival meningioma, 44x30x42 mm (MRI preop - Fig. 1A).
Retrosigmoid approach in combination with presigmoid approach (Fig. 1B), total tumor removal (CT after op - Fig. 1C)

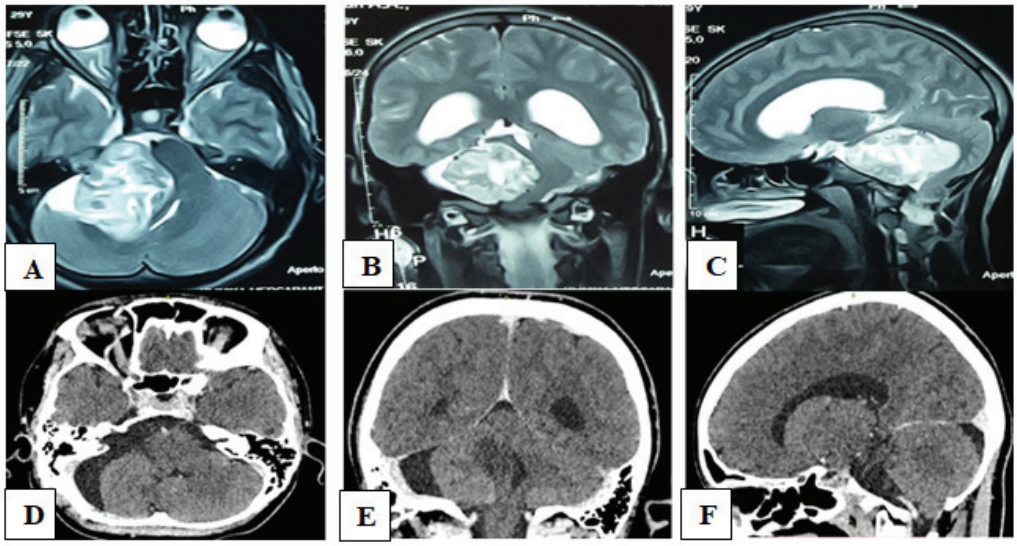

Fig. 2. Vestibular schwannoma, 47x62x41mm (MRI preop - Fig. 2A, B, C).
Retrosigmoid approach, total tumor removal (CT oafter op - Fig. 2D, E, F)

Also we used combination of approaches in foramen jugular schwannomas - these tumors rich large size as they have a long asimptomatic period. Presigmoid approach in this case achive the same purpose early tumor debulking, subtentorial decompression subsequently with safe tumor dissection using retrosigmoid approach. Most important combination of approaches (retrosigmoid and presigmoid) achive avoid trauma of the cerebellum and prevent such complications as meningitis in postop period (no trauma, no edema, no intracerebellum hemorrhage) (Fig. 3).

Endoscopic endonasal transclival approach – 9 cases and endoscopic transoral transclival approach – 2 cases. The clivus and the ventral surface of the brainstem are the most difficul to access in the skull base surgery [14].

Despite the active evolution of various surgical techniques in recent decades, the treatment of the clival tumors and the surrounding anatomical structures is still a challenge for the neurosurgeon [1]. The use of endoscopic endonasal and or transoral transclival approaches provide an access to the ventral surface of the pons, as well as the medulla oblongata, C1, C2 vertebrae [2]. This is especially important for chordoma, chondrosarcoma and extradural tumors with intradural growth (Fig. 4).

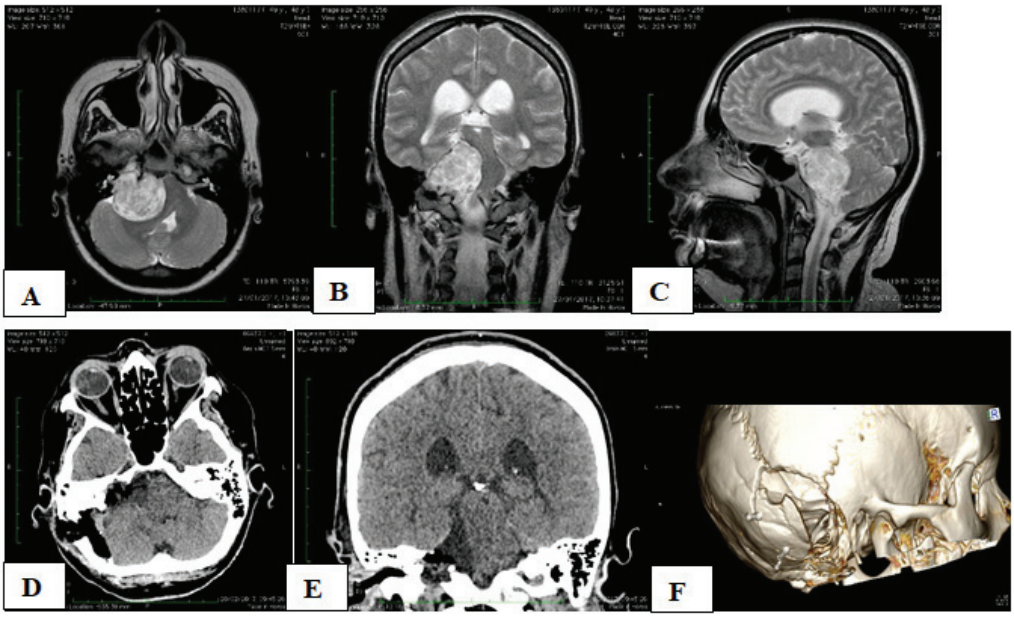

Fig. 3. Foramen jugular schwannoma, 50x39x42 mm (MRI preop - Fig.3A, B, C).
Retrosigmoid approach in combination with presigmoid approach (Fig. 3F), total tumor removal (CT after op - Fig. 3D, E)

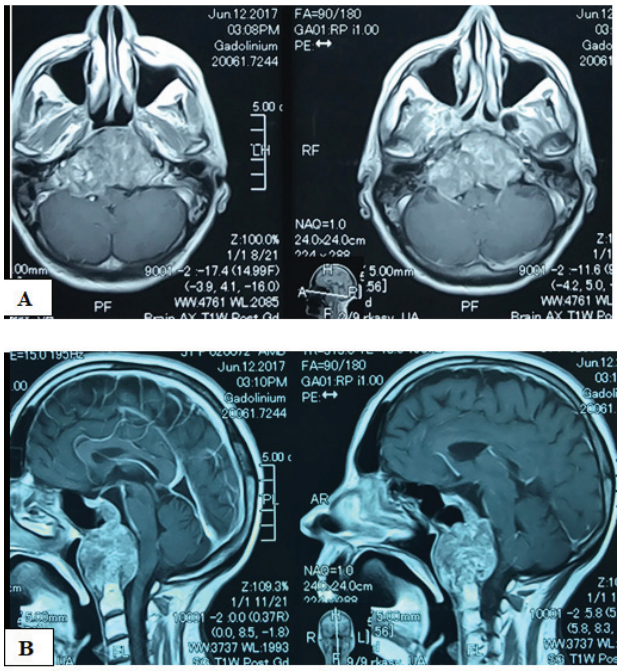

Fig. 4. Clival chordoma, 60x48x42 mm (A, B - MRI preop)

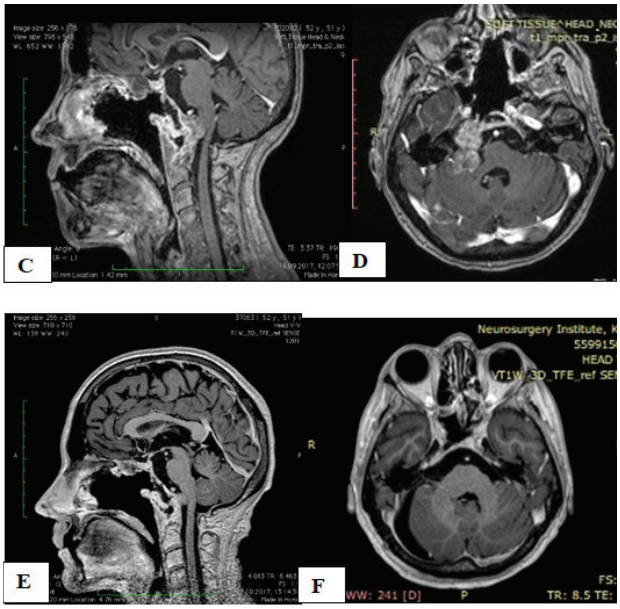

Fig. 4. The same case. MRI after I stage. C,D - Endoscopic endonasal transclival approach.
MRI after II stage. E, F – retrosigmoid approach. Total tumor removal

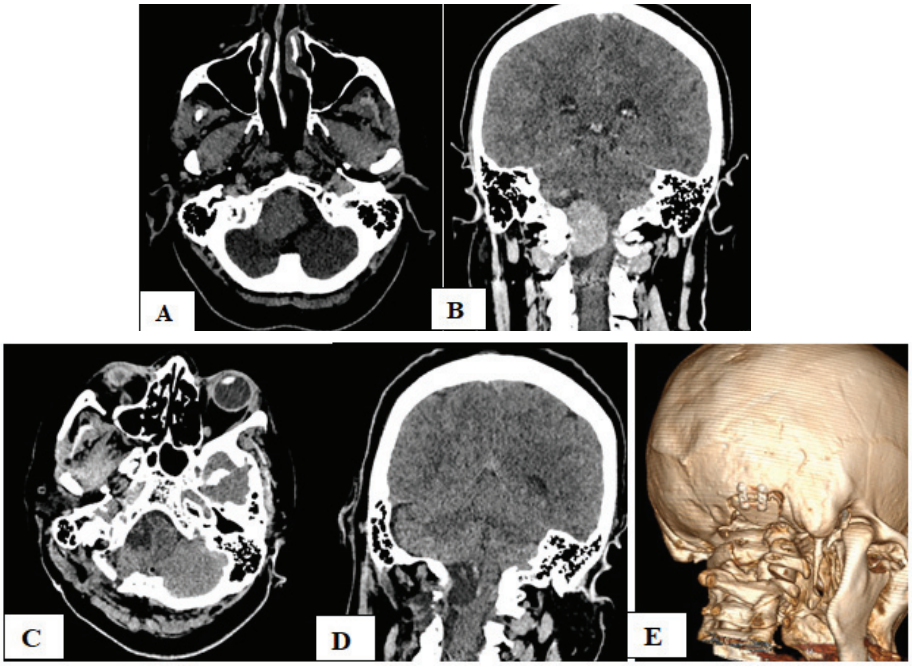

Fig. 5. Foramen magnum meningioma ventro-lateral localization (CT preop - Fig. 5 A, B). The far lateral approach in combination with transcondylar approach and suboccipital retrosigmoid approach. Intraoperative neuromonitoring CN XII. Intraoperative neuromonitoring of pyramidal tracts. Total tumor removal, Simpson II (CT oafter op - Fig. 5 C, D,E)

The far lateral approach was used in 7 cases. The far lateral approach – it is a modification of the traditional lateral suboccipital approcah, which provides adequate exposure of the ventral part cranio-vertebral junction [8], early vessels identification, as well as the absence of any traction on the neuroaxis structures (Fig. 5).

Radicality: There was gross total tumor removal in 49 patients (83%). We performed subtotal tumor removal in 5 patients (8,5%): 4 of them with vestibular schwannomas and 1 patient with foramen jugular schwannoma. We did partial tumor removal in 5 cases (8,5%): 2 patients with clival chordomas; 2 cases with vestibular schwannomas; 1 patient with foramen magnum meningioma.

Complications occurred in 15 patients (25%). Facial palsy of varying manifestations occured in 13 patients (22 %). In 8 of them - temporary, in 3 - permanent, in 2 cases – facial nerve reinnervation done). Meningoencephalitis was observed in 2 cases. Karnofsky scale in patients was ≥70 points, in all of them.

Postoperative mortality observed in 3 patients (5.0%) with large vestibular schwannomas: 1 patient died of cardiac complications (on the background of atrial fibrillation), 2 patients died of meningoencephalitis (10 day and 15 day after surgery, respectively. Bacterial culture - Klebsiella pneumoniae).

Conclusions. 1. The use of ventral craniobasal aprroaches and their combination with posterior-lateral approaches to the large subtentorial tumors allows rapid and early, effective brain stem decompression and subsequent safe and total tumor removal.

2. Ventral decompression of the brain stem structures (endoscopic endonasal and transoral approaches, presigmoid approach, extreme lateral approach) prevents neurological complications thus early patients activation.

3. Neurological complications (facial nerve palsy with diffe - ent manifestations) in most cases was temporary and regressed within 3-12 months.

4. Postoperative mortality of 3 patients - 5.0% (out of 59 patients) can be reduced by intensifying perioperative patient's management.

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SUMMARY

SURGICAL STRATEGY FOR LARGE EXTRACEREBRAL SUBTENTORIAL TUMORS

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Radical surgery over large subtentorial tumors is associated with a high risk of postoperative complications. Despite significant development of imaging technology, intraoperative monitoring, and microsurgical treatment, problems one of tottal and safe large subtentorial tumors removal remain unsolved. The most critical problem relating to large tumors of this localization is postoperative edema. Also brainstem ischemic stroke is not rare and this would partly due to the tumors overgrowthing the vertebral and basilar arteries. Retrospective analysis of 59 patients with large (more than 3 cm) tumors to the posterior cranial fossa operated over 2015-2019 yy. There was gross total tumor removal in 49 (83%) patients; subtotal tumor removal in 5 (8,5%) patients; partial tumor removal in 5 (8,5%) cases. Complications occurred in 15 (25%) patients. The use of ventral craniobasal aprroaches and their combination with posterior-lateral approaches to the large subtentorial tumors allows rapid and early, effective brain stem decompression and subsequent safe and total tumor removal. Ventral decompression of the brain stem structures (endoscopic endonasal and transoral approaches, presigmoid approach, extreme lateral approach) prevents neurological complications thus early patients activation. Postoperative mortality of 3 (5.0%) out of 59 patients can be reduced by intensifying perioperative patient's management.

Keywords: large subtentorial tumors, vestibular schwannomas, petroclival meningiomas, foramen magnum meningiomas, clival chordomas, foramen jugular schwannomas, suboccipital retrosigmoid approach, presigmoid approach, endoscopic endonasal transclival approach, far lateral approach.

РЕЗЮМЕ

ХИРУРГИЧЕСКАЯ СТРАТЕГИЯ ПРИ БОЛЬШИХ ЭКСТРАЦЕРЕБРАЛЬНЫХ СУБТЕНТОРИАЛЬНЫХ ОПУХОЛЯХ

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Радикальная хирургия больших субтенториальных опухолей связана с высоким риском послеоперационных осложнений. Несмотря на значительное развитие технологий визуализации, интраоперационного мониторинга и микрохирургического лечения, одна из проблем тотального и безопасного удаления больших субтенториальных опухолей остается нерешенной. Наиболее острой проблемой при больших опухолях данной локализации является послеоперационный отек. Нередко встречается также ишемический инсульт ствола головного мозга, отчасти из-за того, что опухолью обрастают позвоночные и базилярные артерии. Проведен ретроспективный анализ 59 пациентов с большими (более 3 см) опухолями задней черепной ямки, прооперированных за 2015-2019 гг. Тотальное удаление опухоли выполнено у 49 (83%) пациентов; субтотальное удаление опухоли - у 5 (8,5%) пациентов; частичное удаление опухоли - у 5 (8,5%). Использование вентральных краниобазальных доступов и их комбинации с задне-латеральными доступами к большим субтенториальным опухолям позволяет провести быструю и раннюю эффективную декомпрессию ствола головного мозга с последующим безопасным и полным удалением опухоли. Вентральная декомпрессия структур ствола головного мозга (эндоскопический эндоназальный и трансоральный доступ, пресигмовидный доступ, высокий боковой доступ) предотвращает неврологические осложнения, что способствует ранней активизации пациентов. Послеоперационная летальность может быть снижена за счет интенсификации периоперативного ведения пациентов.

რეზიუმე

ქირურგიული სტრატეგია დიდი ექსტრაცერებრალური სუბტენტორიალური სიმსივნეების შემთხვევაში

ო.პალამარ,ა.გუკ,დ.ოკონსკი,დ.ტესლენკო,. რ.აქსიონოვი

ა. რომოდანოვის სახ. ნეიროქირურგიის ინსტიტუტი, ენდოსკოპიური და კრანიოფარინგიალური ნეიროქირურგიის განყოფილება, კიევი, უკრაინა

დიდი სუბტენტორიალური სიმსივნის რადიკალური ოპერაცია უკავშირდება პოსტოპერაციული გართულებების მაღალ რისკს. ვიზუალიზაციის ტექნოლოგიების, ინტრაოპერაციული მონიტორინგისა და მიკროქირურგიული მკურნალობის მნიშვნელოვანი განვითარების მიუხედავად, დიდი სუბ-

ტენტორიალური სიმსივნის მთლიანი და უსაფრთხო მოცილება სადღეისოდ ერთ-ერთ გადაუჭრელ პრობლემას წარმოადგენს. ამ ლოკალიზაციის მსხვილი სიმსივნის ყველაზე მწვავე პრობლემა პოსტოპერაციული შეშუპებაა. ასევე ხშირია თავის ტვინის ღეროს იშემიური ინსულტი, ნაწილობრივ იმის გამო, რომ სიმსივნე ეხება ხერხემლის და ბაზილარულ არტერიებს. ჩატარდა ქალას უკანა ფოსოს დიდი (3 სმ-ზე მეტი) სიმსივნით 59 პაციენტის რეტროსპექტული ანალიზი, რომლებსაც ოპერაცია ჩაუტარდათ 2015-2019 წწ. აქედან 49 (83%) პაციენტს ჩაუტარდა სიმსივნის ტოტალური რეზექცია, სიმსივნის სუბტოტალური რეზექცია - 5 (8,5%) პაციენტს, სიმსივნის ნაწილობრივი მოცილება - 5 (8,5%).

ვენტრალური კრანიობაზალური მიდგომების და მათი უკანა-ლატრალურ მიდგომებთან კომბინაციის გამოყენება დიდი სუბენტენტორიალური სიმსივნის დროს იძლევა ტვინის ღეროს სწრაფი და ადრეული ეფექტური დეკომპრესიის ჩატარების საშუალებას,რაც უზრუნველყოფს სიმსივნის უსაფრთხო და სრულ მოცილებას. თავის ტვინის ღეროს სტრუქტურების ვენტრალური დეკომპრესია (ენდოსკოპიური ენდონაზალური და ტრანსორალული მიდგომები,პრესიგმოიდული მიდგომა, გვერდითი მაღალი მიდგომა) თავიდან აცილებს ნევროლოგიურ გართულებებს, რაც ხელს უწყობს პაციენტების ადრეულ გააქტიურებას. პოსტოპერაციული სიკვდილიანობა შეიძლება შემცირდეს პაციენტების პერიოპერაციული ინტენსიური მოვლით.

PHOTODYNAMIC THERAPY IN TREATMENT OF PATIENTS WITH PREMALIGNANT VULVAR DISEASES. FIRST EXPERIENCE OF THE METHOD APPLICATION IN UKRAINE

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In recent years, there has been a steady increase in the incidence of vulvar dystrophic diseases, which, according to various sources, occupy from 3% to 10% in the gynecological pathology structure [1]. This pathology, united by the general term "dystrophic diseases", includes lichen sclerosus (lichen, kraurosis), squamous cell hyperplasia (leukoplakia) and vulvar intraepithelial neoplasia (VIN) [2]. The lichen sclerosus is the main manifestation of squamous cell hyperplasia - a dystrophic disease including lesions of stratified flat non-keratinized epithelium. VIN is a premalignancy characterized by lesions of stratified squamous epithelium with impaired stratification without affecting the basement (basic) membrane in the pathological process [1]. This group of diseases is characterized by a fairly high risk of malignant transformation: according to various sources the risk of malignancy against the background of kraurosis and lichen sclerosus ranges from 5% to 9%, for VIN - from 6% to 18%, and when both processes are combined - over 50% [3].

Conventionally, all treatment methods for lichen sclerosus and VIN can be subdivided into conservative and surgical.

So far, the main approach in squamous cell hyperplasia treatment is vulvectomy with histological verification of the removed foci. Laser CO_2 coagulation/vaporization, high-intensity focused ultrasound therapy have certain therapeutic potential. Despite the relatively high effica , surgical intervention is connected with trauma, risk of complications and unsatisfactory cosmetic results (in a certain percentage of cases). The use of laser and ultrasound technologies does not allow have an effect on the etiopathogenetic mechanisms of the disease development. It is also worth noting that the frequency of local recurrences remains high: according to Mahner S., when using operational equipment, at least 30%; with laser or ultrasound use - from 15 up to 48% - according to Hillemanns P. [4, 5].

Thus, non-conservative methods of VIN treatment include surgical intervention: in case of VIN Grade II and III at reproductive age, for the patients with a large area of pathologically altered tissues, either surgical excision within normal tissues or superficial vulvectomy with plastic reconstruction of the defect can be performed. However, in comparison with other methods of treatment, surgical intervention is traumatic, having high rate of postoperative complications and, in some cases, poor functional and cosmetic results [6].

Electrocoagulation using high-frequency RF range currents has a certain therapeutic potential. However, this method of treatment is characterized by poorly-controlled depth of impact on pathological tissues, frequent local recurrences and complications (cicatricial deformities, non-healing lesions, etc.) [6].

It is also possible to use the cryodestruction method, but at the same time, the use of liquid nitrogen has a negative effect on the skin recovery processes and is characterized by a long healing period of the wound surfaces [6].

It is worth to mention the use of high-energy CO_2 lasers in the treatment of VIN. Despite the relatively high therapeutic efficacy of this method, its serious disadvantages include likelihood of bleeding during the removal of large areas of pathological foci, development of scarring processes and high percentage of local recurrences [6].

A certain role in the treatment of VIN is given to the use of 5% *Imiquimod* cream (especially for hyper-pigmented forms of the disease). However, in some cases, the resistance to the use of this medication and relatively high rate of local recurrences are noted [7].

All this underlines the necessity to search for new methods of treatment for this pathology. One of them is *photodynamic therapy* (PDT) – a treatment method based on the local or systemic (intravenous) introduction of a special medicinal product called photosensitizer (PS) into the patient's body with subsequent irradiation of pathologically altered tissues with laser radiation having specific wavelength. PS has the ability to accumulate se-

lectively in the tumor or pathologically altered tissues, and the process of their irradiation triggers a cascade of complex photochemical reactions in the tumor cell. These reactions are associated with the toxic effect of the resulting active oxygen forms leading to its death. PDT can have both a direct cytotoxic effect - resulting in apoptosis and autophagy of the tumor cell - and an indirect one, associated with impaired blood supply to the tumor tissue and subsequent ischemic necrosis [8].

The main objective of this research is clinical approbation, assessment of the tolerability and efficac of using the PDT method in patients with vulvar premalignancies.

Material and methods. The study included 10 patients with morphologically verified diagnoses of "intraepithelial vulvar neoplasia (VIN-II)", mixed vulvar dystrophy (lichen sclerosus and squamous cell hyperplasia) and "in-situ vulvar cancer". The patients' age range was 31 to 67 (average age was 53.3 ± 3.6 years). The diagnosis was established on the basis of the medical history, clinical examination and patients' complaints, vulvoscopy and morphological (histological and/or cytological) examination of pathologically altered vulvar tissues. The main criteria for the inclusion of patients in the PDT study were histological and cytological confirmation of the diagnosis, the absence of severe comorbidity and the written consent to the treatment.

All therapeutic and diagnostic manipulations were carried out after the patients were provided with full information about the photosensitizer, the PDT method, possible benefits, risks, adverse reactions and complications, as well as the duration of follow-up visits and compliance with remedial recommendations. All the patients signed a written consent for the PDT treatment. All manipulations were performed in accordance with the Helsinki Declaration of the World Medical Association (1964, revised in 2013).

Fotolon® medicinal product (produced by *Belmedpreparaty* Pharmaceutical Company, the Republic of Belarus) - which is trisodium Ce6 chlorin salt complex with low molecular polyvinylpyrrolidone - was used as a PS. It was dissolved in 200 ml of physiological saline and was being injected intravenously over 30 minutes at doses of 1 to 2.5 mg per 1 kg of a patient's body weight in low-light conditions.

A PDT session was performed 3 hours after finishing the PS infusion using the *Lika-surgeon* versatile laser coagulator (made by *Fotonica Plus*, Ukraine, $\lambda = 660$nm). The size of photo-irradiation areas (fields) varied from 1 to 3 cm, the number of the areas ranged from 2 to 5, the radiation power was 0.4 W, the exposure dose of light varied from 100 to 150 J/cm^2. The duration of the session depended on the degree of prevalence of pathological foci and lasted 10-30 minutes depending on the number of radiation areas. Normal tissues of the vulva with a minimum distance of 5 mm from the edges of the affected areas were included in the photo-irradiation area. Due to high sensitivity of the photo-irradiation areas, non-narcotic analgesic medications were premedicated 15-30 minutes before the PDT session to relieve the pain (*dexalgin* 50 mg/2 ml, 2 ml ampulla; *ketolong* 3% 30 mg/ml, 1 ml ampulla; *nalbufin* 10 mg/ml, 1 ml ampulla).

The tolerability of PDT was evaluated based on the frequency and severity of adverse reactions and complications of the treatment carried out based on the analysis of the CTCAE criteria (version 3.0).

Evaluation of the PDT efficac was made based on the presence/absence of complaints, visual observation data about the change in the area of the treated pathological foci and using the data of the morphological study conducted 3 and 6 months after the treatment (The WHO criteria):

• complete regression (CR) - absence of all signs of the disease after 100% regression of pathological foci 3 months after PDT, confirmed 6 months after the treatment

• partial regression (PR) - a decrease in the total size of pathological foci by 50% or more, followed by stabilization, established in 3 months and confirmed 6 months after the PD session;

• Absence of effect (AE) - a decrease in the total area of the pathological foci by less than 50%, a state without a decrease or increase in the area of the pathological foci.

Results and discussion. In 100% of the cases, no symptoms of skin photo-toxicity (itching, hyperemia of open skin areas, soft facial tissues swelling, etc.) were recorded. During intravenous infusion of PS and the period of time before the PDT session, the general condition of the patients was satisfactory. There were no cases of allergic reactions accompanied by pronounced dysfunction of vital organs (such as angioedema, urticaria, arterial blood pressure fall, bronchospasm, etc.). Despite the premedication procedure performed prior to the PDT session, all the patients had a moderately pronounced pain syndrome (I-II degree). During the post-procedure period, analgesics were prescribed to all patients (*dexalgin* 50 mg/2 ml, 2 ml ampulla; *ketolong* 3% 30 mg/ml, 1 ml ampulla; *nalbufin* 10 mg/ml, 1 ml ampulla).

After the end of the PDT session, all the patients had a moderately pronounced edema in the areas of photo-irradiated pathological tissues. Within 1-5 days after the treatment, dark brown or black photochemical necrosis area started to form.

During the follow-up observation, conducted 3 and 6 months after the session, remission of clinical symptoms of the disease (vulvar itching) in the treated pathological foci was observed in patients with premalignant vulvar diseases (in all 10 cases).

The data on the clinical and morphological efficac of the PDT treatment method are presented in Table.

It is worth noting that the lack of PDT efficac in 3 cases is associated with the use of subtherapeutic doses of Fotolon® PS (1 mg/kg). That is the reason why a lack of treatment efficac (PR or AE) was recorded in these patients. The use of therapeutic doses of PS and 130 J/cm^2 or higher photo-irradiation exposure doses allowed to achieve both clinical and morphological CR 3 and 6 months after the treatment.

During the control (follow-up) study conducted in 3 months, the following results were recorded for the patients with VIN grade II (clinical) CR were recorded in 40% of cases (n=2), PR - 40% (n=2), AE - 20% (n=1); (morphological) CR - 60% (n=3), AE - 40% (n=2). The presence of PR and AE is attributed to the use of subtherapeutic PS dose.

During the control study conducted in 6 months, the following results were recorded for the patients with VIN grade II (clinical) CR were recorded in 60% of cases (n=3), PR - 20% (n=1), AE - 20% (n=1); (morphological) CR - 60% (n=3), AE - 40% (n=2). The presence of PR and AE is attributed to the use of subtherapeutic PS dose.

Two patients with mixed vulvar dystrophy after 3 and 6 months had both clinical and morphological CR (with PS dose of 2.5 mg/kg and exposure doses of 150 J/cm^2). Within the specified time period, PR was noted in 1 patient due to the prevalence of the pathological process and the use of a subtherapeutic dose of PS (1 mg/kg).

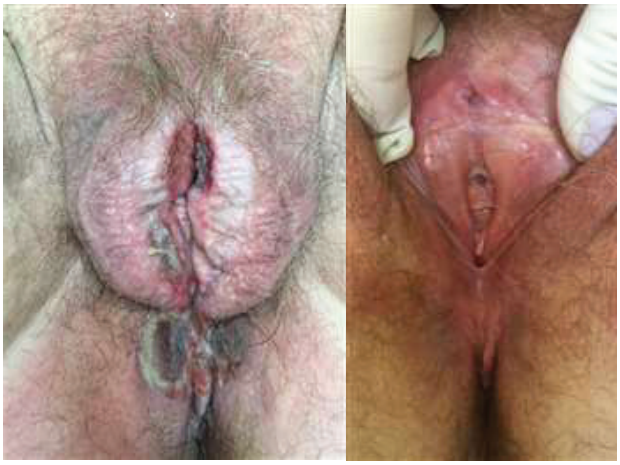
After 3- and 6-month terms both clinical and morphological CR (with PS dose of 2.5 mg/kg and exposure doses of 130-150 J/cm^2) were noted in 2 patients with vulvar cancer in-situ.

The results obtained are graphically illustrated in Figures 1, 2, 3.

Table. Results of the PDT treatment in the patients with vulvar pathology

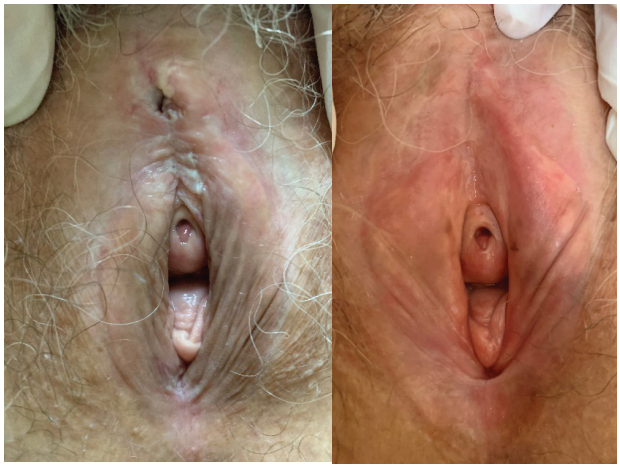
Patient	Age, years	Clinical diagnosis	Fotolon dose, mg/kg	Irradiation dose, J/cm²	Efficacy*			
					clinical		morphological	
					in 90 days	in 180 days	in 90 days	in 180 days
B.	67	VIN grade II	2,5	150	PR	CR	CR	CR
T.	51	VIN grade II	1	100	AE	AE	AE	AE
P.	56	VIN grade II	2,5	130	CR	CR	CR	CR
Yu.	31	Mixed vulvar dystrophy	1	100	PR	PR	PR	PR
S.	58	Mixed vulvar dystrophy	2,5	100	CR	CR	CR	CR
P.	58	Vulvar cancer in situ	2,5	150	CR	CR	CR	CR
P.	50	Mixed vulvar dystrophy	2,5	130	CR	CR	CR	CR
D.	37	Vulvar cancer in situ	2,5	150	CR	CR	CR	CR
Sh.	63	VIN grade II	1	150	PR	PR	AE	AE
Ch.	62	VIN grade II	2,5	150	CR	CR	CR	CR

** CR - complete regression; PR - partial regression; AE – absence of effect*



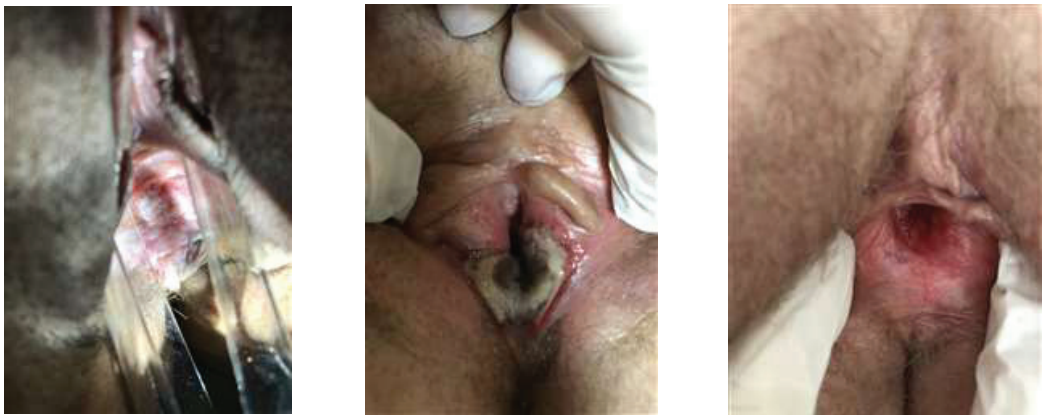
A *B*

Fig. 1. Patient S., 70 years old. Clinical diagnosis: lichen sclerosus. A - 7 days after PDT (100 J/cm²); B - 3 months after PDT



A *B*

Fig. 2. Patient T., 61 years old. Clinical diagnosis: mixed vulvar dystrophy (lichen sclerosus and squamous cell hyperplasia) A - before PDT; B - 3 months after PDT(100 J/cm²)



A *B* *C*

Fig. 3. Patient D., 37 years old. Clinical diagnosis: Ca in situ vulvar vestibule. A - before PDT; B - 7 days after PDT (150 J/cm²); C - 3 months after PDT

All the patients who underwent PDT treatment should follow the following recommendations:

compliance with the daylight restriction mode for 3-4 days;

adequate pain treatment (*dexalgin* 50 mg/2 ml, 2 ml ampulla; *ketolong* 3% 30 mg/ml, 1 ml ampulla; *nalbufin* 10 mg/ml, 1 ml ampulla); hygiene; sexual continence; rapid epithelialization medications (10% Synthomycin liniment for 1-2 weeks; Methyluracil with Miramistin ointment for 3-4 weeks).

Conclusion. The results obtained in foreign studies testify to the fact that the PDT method is a well-tolerated and rather effe - tive option of organ-preserving treatment of patients with vulvar lichen sclerosus and different grades of VIN. At the moment, the results of a number of papers showing the positive aspects of using PDT with various classes of photosensitizing agents (including 5-aminolevulinic acid and its derivatives, chlorine PS, etc.) have been published. The authors noted a rather high occurrence of complete clinical and morphological regressions when using PDT in these categories of patients [9, 10, 11, 12, 13, 14].

In view of the small sample of patients, the results obtained in our study at the moment do not allow us to draw far-reaching conclusions. However, it is possible to state that the PDT method is a well-tolerated and potentially effective option for treating patients with vulvar lichen sclerosus and VIN [16,17].

It seems expedient to streamline photo-irradiation regimes of pathologically altered tissues and to determine the main indications for using the PDT method in these categories of patients.

In our opinion, the main indications for the use of PDT in the treatment of vulvar lichen sclerosus and VIN are

• histologically verified diagnosis
• any degree of severity (grade I, II, III) or prevalence of the pathological process;
• inefficiency of previously applied treatment method
• presence of contra-indications to the use of traditional methods of treatment;
• refusal of a patient from surgical intervention.

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SUMMARY

PHOTODYNAMIC THERAPY IN TREATMENT OF PATIENTS WITH PREMALIGNANT VULVAR DISEASES. FIRST EXPERIENCE OF THE METHOD APPLICATION IN UKRAINE

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The aim of the study is to evaluate the tolerability and effe - tiveness of photodynamic therapy (PDT) of patients with premalignant diseases of the vulva.

The study was performed on 10 patients on the basis of the National Cancer Institute of Ukraine (Kyiv). The age of patients ranged from 31 to 67 years old (mean age: 53.3±3.6 years old). The diagnosis was made on the basis of medical history, complaints and clinical examination of patients, vulvoscopy and the

results of morphological examination of pathologically altered vulvar tissues. A drug of the chlorine series “Photolon” (RUE “Belmedpreparaty”, Republic of Belarus) in doses from 1 to 2.5 mg/kg was used as a photosensitizer (FS). Photoirradiation of pathologically altered foci was performed 3-4 hours after the end of the infusion of FS using a laser coagulator universal “Lika-surgeon” (“Photonics Plus”, Ukraine, λ = 660 nm) with a radiation power of 0.4 W in exposure doses of 100 up to 150 J/cm^2. PDT tolerability was assessed basing on the frequency and severity of adverse reactions (CTCAE, version 3.0). The effe - tiveness of PDT was assessed basing on the presence / absence of complaints, data from visual observation of changes in the area of treated lesions and morphological examination data at 3 and 6 months after treatment (WHO criteria).

No serious adverse reactions associated with the introduction of FS and PDT session were observed: no allergic reactions (Quincke’s edema, urticaria, drop in blood pressure, bronchospasm), no symptoms of skin phototoxicity. In the specified control patients’ observation terms, the remission of disease clinical symptoms (an itch in the area of vulva) in the treated pathological centers as well as high frequency of clinical and morphological regressions were noted.

The obtained results indicate the relevance and prospects of further research in the field of laser technology and PDT as options for organ-preserving treatment of premalignant diseases of vulva.

Keywords: photodynamic therapy, patients, premalignant vulvar diseases.

РЕЗЮМЕ

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ЛЕЧЕНИИ БОЛЬНЫХ С ПРЕДРАКОВЫМИ ЗАБОЛЕВАНИЯМИ ВУЛЬВЫ. ПЕРВЫЙ ОПЫТ ПРИМЕНЕНИЯ МЕТОДА В УКРАИНЕ

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Цель исследования - оценить переносимость и эффективность метода фотодинамической терапии в лечении пациентов с предраковыми заболеваниями вульвы.

Исследование выполнено на 10 пациентах на базе Национального института рака Украины (Киев). Возраст пациентов варьировал в пределах от 31 до 67 лет (средний возраст 53,3±3,6 г.). Диагноз поставлен на основании анамнеза, жалоб и клинического осмотра пациентов, вульвоскопии и результатов морфологического исследования патологически измененных тканей вульвы. В качестве фотосенсибилизатора (ФС) использовали препарат хлорного ряда «Фотолон» (РУП «Белмедпрепараты», Республика Беларусь) в дозах от 1 до 2,5 мг/кг. Фотооблучение патологически измененных очагов проводили спустя 3-4 часа после окончания инфузии ФС на универсальном лазерном коагуляторе «Лика-хирург» («Фотоникс Плюс», Украина, λ = 660 нм) с мощностью излучения 0,4 Вт и дозой облучения от 100 до 150 Дж/см^2. Переносимость фотодинамической терапии (ФДТ) оценивали по частоте и тяжести побочных реакций (CTCAE, версия 3.0). Эффективность ФДТ оценивалась на основании наличия/отсутствия жалоб, данных визуального наблюдения за изменениями в области обработанных поражений и данных морфологического исследования спустя 3 и 6 месяцев после лечения (критерии ВОЗ).

Серьезных побочных реакций, связанных с введением ФС и сеанса ФДТ, не наблюдалось: аллергических реакций (отек Квинке, крапивница, падение артериального давления, бронхоспазм) и симптомов фототоксичности кожи не выявлено. В указанные контрольные сроки наблюдения пациентов отмечались ремиссия клинических симптомов заболевания (зуд в области вульвы) в пролеченных патологических очагах, а также высокая частота клинических и морфологических регрессов.

Полученные результаты указывают на актуальность и перспективность дальнейших исследований в области лазерных технологий и ФДТ как вариантов органосохраняющего лечения предраковых заболеваний вульвы.

რეზიუმე

ფოტოდინამიკური თერაპია ვულვის კიბოსწინარე დაავადებების მკურნალობაში. მეთოდის გამოყენების პირველი გამოცდილება უკრაინაში

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კვლევის მიზანს წარმოადგენდა ფოტოდინამიკური თერაპიის მეთოდის ამტანობის და ეფექტურობის შეფასება პაციენტებში ვულვის კიბოსწინარე დაავადებებით.

გამოკვლეულია 10 პაციენტი უკრაინის კიბოს ეროვნული ინსტიტუტის ბაზაზე (უკრაინა). პაციენტების ასაკი მერყეობდა 31-დან 67 წლამდე (საშუალო ასაკი - 53,3±3,6 წ.). დიაგნოზი დადგენილი იყო ანამნეზის, ჩივილების, პაციენტების კლინიკური დათვალიერების, ვულვოსკოპიის და ვულვის პათოლოგიურად შეცვლილი ქსოვილების მორფოლოგიური კვლევის საფუძველზე. ფოტოსენსიბილიზატორის სახით გამოყენებული იყო ქლორის რიგის პრეპარატი “ფოტოლონი” (“ბელმედპრეპარატი”, ბელარუსისი რესპუბლიკა), დოზით 1-2,5 მგ/კგ. პათოლოგიურად შეცვლილი კერების ფოტოდასხივება ტარდებოდა ფოტოსენსიბილიზატორის ინფუზიის დასრულებიდან 3-4 საათის შემდეგ უნივერსალურ ლაზერულ კოაგულატორზე “ლიკა-ქირურგი” (“ფოტონიქს პლიუსი”, უკრაინა, λ = 660 нм), დასხივების სიმძლავრით 0,4 ვტ და დასხივების დოზით 100 - 150 ჯ/სმ^2. ფოტოდინამიკური თერაპიის ამტანობა ფასდებოდა გვერდითი რეაქციების სიხშირით და სიმძიმით. ფოტოდინამიკური თერაპიის ეფექტურობა ფასდებოდა ჩივილების არსებობა/არარსებობის, დამუშავებულ დაზიანებებზე ვიზუალური დაკვირვების და მორფოლოგიური კვლევის შედეგების საფუძველზე მკურნალობიდან 3 და 6 თვის შემდეგ (ჯანმო-ს კრიტერიუმებით).

ფოტოსენსიბილიზაციასთან და ფოტოდინამიკურ

თერაპიასთან დაკავშირებული სერიოზული გვერდითი რეაქციები არ აღინიშნა: ალერგიული რეაქციები (კვინკეს შეშუპება, ჭინჭრის ციება, არტერიული წნევის დაცემა, ბრონქოსპაზმი) და კანის ფოტოტოქსიურობის სიმპტომები არ გამოვლენილა. პაციენტებზე დაკვირვების საკონტროლო ვადებში აღინიშნებოდა დაავადების კლინიკური სიმპტომების რემისია (ქავილი ვულვის მიდამოში) ნამკურნალებ პათოლოგიურ უბნებში, ასევე, კლინიკური და მორფოლოგიური რეგრესიის მაღალი სიხშირე.

მიღებული შედეგები მიანიშნებს შემდგომი კვლევების აქტუალობის და პერსპექტულობის შესახებ ლაზერული ტექნოლოგიების და ფოტოდინამიკური თერაპიის სფეროში, როგორც ვულვის კიბოსწინარე დაავადებების ორგანოშემანარჩუნებელი მკურნალობის ვარიანტებისა.

TEMPORAL TRENDS OF CERVICAL CANCER MORTALITY IN GEORGIA, 2011-2018

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Cervical cancer (CC) represents the fourth most common cancer and the fourth leading cause of cancer-related mortality in women worldwide [3]. Additionally, more than 90% of deaths occur in developing countries, where women are 18 times more likely to die from CC than women in developed countries [4]. CC is considered a neglected neoplasm in low-income countries, where early detection by screening methods for Pap test inaccessible, which allows to identify the disease at early stages, when treatment is effective [7]. Cervical cancer screening, with high coverage of the target population, is correlated with reduced CC morbidity and mortality and increased survival rates in developed countries [6,9].

Cervical cancer is the fifth most common cancer diagnosed among women in Georgia, after breast, thyroid, colorectal, and uteri cancers. During 2015-2018, annual number of new cervical cancer cases, reported to the Georgian population-based cancer registry were 344, 371, 254 and 276; it composed 17.9, 19.6, 15.0 and 14.3 per 100000 female population accordingly. Cervical cancer incidence risk increases greatly from the age of 40-44 years, peaks in the 50-60 age group and decreases after the age of 75.

The study aims to describe cervical cancer mortality in Georgia during the period of 2011 and 2018.

Material and methods. Descriptive analysis was conducted using mortality data during the period of 2011-2018 from the National Statistics Offic of Georgia. Taking into consideration that during 2005-2010 annual number of registered deaths from cervical cancer in Georgia was quite low (varied between 50 and 60 cases), this time period was not included in the analysis. The study population consisted of all deaths caused by cervical cancer (ICD 10, C53) among women within the age range of 25 and over; due to the fact that cervical cancer mortality under 25 years are extremely rare in Georgia (only one case of mortality was registered during the period of 2011-2018), mortality within this age group was excluded from the analysis; To estimate time trends study period was divided into two groups - 2011-2014 and 2015-2018 years. For data analysis, descriptive statistics was performed, in which the mortality rates, age-specific mortality rates per 100,000 female population and other statistical measurements – median, the first quartile ($Q_{1,}$ the age point, below which lies 25% of death), the third quartile ($Q_{3,}$ the age point, over which lies 25% of death), and interquartile range (IQR, the age interval, in which falls 50% of all deaths) of age at death from Cervical cancer were estimated. The age-specific mortality rates per 100 000 female population were calculated for twelve different age groups (25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80 and over) in eight years, mentioned above. Statistical analysis was completed by using the programs of EpiInfo version 7 and Statistical Package of the Social Science (SPSS) version 15 for Windows. The statistical significance tests - *p value*, and 95% of Confidence Interval (95% CI), were used in order to estimate statistical reliability of the results.

Results and discussion. Totally 1231 cases of CC deaths were registered during the period of 2011-2018 in Georgia. The number of annual deaths varied between 121 and 185 cases, that composed variation of mortality rates from 6.1 to 9.5 per 100 000 women. Maximum mortality rate was reported in 2016 (Table 1). According to the 95% of CI the difference between mortality rates according to calendar years is not statistically significant

Cervical cancer mortality increases with age. The age effects for almost all calendar years included in analysis (2011-2018) presented an increasing trend with age from 25 to 59, while a moderate decrease was shown within the age group from 60-64 to 65-69 and over 80 years of old (Tables 2, 3).

The median age of deaths from CC has no tendency to increase or decrease, it fluctuated inconsistently between 57 and 62 years during the study period; in most of the years studied, one quarter of all deaths occurred within the age group 25-52 years. The interquartile range of CC deaths, or age range within which occurred about 50% of all deaths was quite narrow and equaled to 47-67, 52-72, or 52-67 years in different calendar years (Table 4).

Comparison of age-specific mortality rates within of the two 4-year periods - 2011-2014 and 2015-2019 - by using the One Way ANOVA test, revealed that the difference was not statistically significant (*p value* >0.05). Mean age-specifi mortality rates for the periods of 2011-2014 and 2015-2018 were 11.7 (SD=7) and 14.1 (SD=6.6) accordingly and presented a slight increase.

Table 1. Cervical cancer mortality rates per 100000 women and 95% of Confidence intervals, 2011-2018, Georgia

Statistical measurements	Years							
	2011	2012	2013	2014	2015	2016	2017	2018
number of deaths	121	142	136	158	166	185	157	166
mortality rates	6.1	7.3	6.9	8.1	8.5	9.5	8.1	8.6
95% CI	5.1-7.3	6.1-8.5	5.9-8.2	6.9-9.5	7.3-9.9	8.2-10.9	6.9-9.4	7.3-9.9

Table 2. Cervical cancer Age-specific mortality rates per 100000 women and 95% of confidence intervals, 2011-2018

Rate/ 95%CI	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
2011												
rate	**0.7**	**4.6**	**6.2**	**4.7**	**9.8**	**9.7**	**14.2**	**18.3**	**7.2**	**12**	**12.6**	**9.0**
95% CI	0.04-3.5	1.9-9.5	2.9-11.8	1.9-9.7	5.6-16.1	5.5-16	8.9-22	11.5-27.8	2.6-16	6.7-20	6.2-23.2	3.9-17.8
2012												
rate	**0**	**0.8**	**4.7**	**9.5**	**9.5**	**11**	**15.6**	**9.7**	**11.4**	**24.3**	**32.1**	**7.7**
95% CI	0	0.04-3.8	1.9-9.8	5.1-16.2	5.3-16.0	6.5-17.5	9.8-23.7	5.1-16.9	5.3-21.6	16.1-35.0	21.0-47.0	3.1-15.9
2013												
rate	**0**	**0.8**	**3.9**	**7.2**	**9.2**	**15.8**	**13.9**	**13.8**	**11.6**	**14.2**	**13.8**	**2.4**
95% CI	0	0.04-3.8	1.4-8.7	3.5-13.2	5.0-15.6	10.3-23.3	8.5-21.5	8.2-22	5.7-21.4	7.9-23.6	7.3-24	1.5-3.7
2014												
rate	**0.7**	**0.8**	**2.4**	**5.2**	**12.6**	**15.9**	**14.3**	**14.4**	**17.2**	**24.1**	**17.8**	**2.0**
95% CI	0.04-3.5	0.04-3.7	0.6-6.4	9.6-16.3	7.5-20	10.3-23.4	8.9-22	8.7-22.6	10-27.7	15-37	10.3-28.6	1.2-3.2
2015												
rate	**0**	**0**	**7.1**	**13.7**	**12.9**	**15.6**	**25.7**	**12.5**	**18.6**	**11.7**	**18.2**	**1.2**
95% CI	0	0	3.5-13	8.2-21.5	7.6-20.5	10-23.2	18.2-35.4	7.3-20.1	11.4-28.8	5.4-22.2	10.8-28.9	0.6-2.3
2016												
rate	**0**	**1.5**	**5.5**	**11.4**	**16.3**	**16.1**	**23.8**	**19.6**	**17.4**	**27.1**	**22.6**	**1.0**
95% CI	0	0.2-4.9	2.4-11	6.5-18.6	10.3-24.8	10.4-24	16.7-33.1	12.9-28.8	10.6-26.9	16.3-42.5	14.2-34.2	0.5-1.9
2017												
rate	**0**	**0.73**	**4.7**	**9.8**	**14.8**	**15.3**	**15.7**	**16.1**	**19.5**	**15.7**	**15.4**	**1.7**
95% CI	0	0.04-3.6	1.9-9.8	5.3-16.6	9.0-23.0	9.6-23	10-23.4	10.1-24.4	12.4-29.3	7.9-27.9	8.6-25.7	0.9-2.8
2018												
rate	**0.75**	**3.7**	**6.3**	**10.65**	**0**	**16.7**	**23.4**	**19.8**	**20.8**	**11.3**	**17.3**	**1.9**
95% CI	0.04-3.7	1.3-8.2	2.9-12	5.9-17.8	0	10.6-25.1	16.4-32.5	13.1-28.8	13.5-30.7	5.3-21.5	9.6-28.8	1.1-2.9

Table 3. Mean age-specific mortality rates and standard deviations (SD), 2011-2018

mean rates /SD	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
Mean	0.23	1.6	5.1	8.7	10.6	14.5	18.6	15.8	15.7	18.5	18.9	14.9
SD	0.4	1.6	1.4	3.1	5.0	2.5	4.8	3.4	4.5	6.8	5.8	5.8

Table 4. Median, Quartiles (Q_1 and Q_3), and Interquartile Range (IQR) of age at death from Cervical cancer, 2011-2018

Statistical measurements	Years							
	2011	2012	2013	2014	2015	2016	2017	2018
median age	57	62	59.5	62	57	57	57	62
Q_1 of age	47	52	52	52	47	52	52	52
Q_3 of age	67	72	72	72	67	67	67	67
IQR of age	20	20	20	20	20	15	15	15

In May 2018, the Director-General of WHO announced a global call to action towards the elimination of cervical cancer. This initiative is the first worldwide health strategy for the elimination of cancer. Key indicators and short-term targets to control both cervical cancer incidence and mortality are being developed for the period 2020–2030, which will define the pathway of elimination for all countries. Prevention and control measures, such as vaccination against *Human papilloma virus* (HPV) and screening for cervical cancer allow to be achieved this very ambitious goal. Screening programs promote not only early detection of disease, but it helps to reduce the incidence, if adequate treatment of pre-cancer disorders, detected during the screening, is implemented.

Cervical cancer elimination targets by 2030, defined by the WHO expert group known as the 90-70-90, which means that 90% of girls fully vaccinated with HPV vaccine by 15 years of age; 70% of women screened for CC at 35 and 45 years of age and almost 90% of pre-cancer disorders, detected during the screening, managed appropriately.

Current status of prevention and control of cervical cancer globally is as follows: The proportion of countries where vaccination against HPV is implemented varies widely according to the level of development of the countries. 84% of high income countries have introduced the vaccine, while this fraction in middle- and low-income countries is quite low and equals to 31% and 12% respectively; *Human papilloma virus* is the cause of 630,000 cancers annually, 83% of which are cervical cancers, 10.9% other anogenital, and 4.6% oropharyngeal cancers. Two HPV vaccines, a bivalent and a quadrivalent vaccine, have been available since 2006. In addition, in 2015 a third vaccine, a nonavalent vaccine was introduced; The HPV vaccines are highly effective and safe, they are primarily used for young adolescent girls, but it is also recommend for boys aged 12-13 and given as a three-dose or a two-dose series. These vaccines, combined with organized screening, have a real potential to avoid millions of cervical cancer new cases and deaths over the coming decades globally (1, 2, 8, 10).

There is a big disparities among the countries according to the screening and treatment for pre-cancerous lesions: only 22 highly developed countries reported CC screening programs achieving 70% or above coverage of target population. This coverage level ensures to realize a reduction of cancer early mortality. However the majority of countries report participation rates below 50%, some as low as 10%. The reasons of low coverage may vary by country, but major issues are related to fragmented service delivery, unavailable infrastructure, lack of human resources, low awareness of population, and limited financial resources (4, 5).

The state screening program for cervical cancer was implemented in 2011 in Georgia; women aged 25-60 years with a 3-year recall interval are invited for a screening. As in other developing countries coverage rate of target population is still a major challenge, mean rates vary among 10% and 25% across the regions of the country. In Georgia vaccination against *Human papilloma virus* have been included in the national vaccination program in 2019, target population are girls 10-11-12 years of age. Vaccination had a good starting rates, especially in regions 69% in Adjara vs. 18% in Tbilisi. Finally, key tools for cervical cancer prevention - screening and vaccination - are implemented in the country; now we need mobilization of all human, financial and intellectual resources in order to join the global call and promote cervical cancer elimination in our country.

Conclusions: The study revealed a slight increase in CC mortality, which could be related to the improvement of death registration. Comparatively stable median age of deaths, indicates that, there is no tendency of cervical cancer early mortality reduction in Georgia.

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SUMMARY

TEMPORAL TRENDS OF CERVICAL CANCER MORTALITY IN GEORGIA, 2011-2018

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Cervical cancer is the fifth most common cancer diagnosed in Georgia, after breast, thyroid, colorectal, and uteri cancers. During 2015-2018 cervical cancer incidence composed 17.9, 19.6, 15.0 and 14.3 per 100000 female population accordingly.

The study aims to describe cervical cancer (CC) mortality in Georgia during the period of 2011 and 2018.

Descriptive analysis was conducted using mortality data during the period of 2011-2018 from the National Statistics Offic of Georgia. To estimate time trends of CC mortality study period was divided into two groups - 2011-2014 and 2015-2018 years. For data analysis, descriptive statistics was performed, in which the mortality rates, age-specific mortality rates per 100,000 female population and other statistical measurements – median, the first quartile (Q_1), the third quartile (Q_3), and interquartile range (IQR) of age at death from Cervical cancer were estimated. Statistical analysis was completed by using the programs of EpiInfo version 7 and Statistical Package of the Social Science (SPSS) version 23 for Windows. The statistical significance tests - *p value*, and 95% of Confidence Interval (95% CI) were used in order to estimate statistical reliability of the results.

The number of annual deaths varied between 121 and 185 cases that composed variation of mortality rates from 6.1 to 9.5 per 100,000 women. According to the 95% of CI the difference between mortality rates according to calendar years is not statistically significant. Mean mortality rates for the periods 2011-2014 and 2015-2018 were 7.1(SD=0.7) and 8.7 (SD=0.5) accordingly and presented a slight increase. Taking into consideration that during 2005-2010 annual number of registered deaths from cervical cancer in Georgia was quite low and varied between 50 and 60, it is likely that this increase is related to the improvement in registration and is not a true increase. Therefore, the second period (2015-2018) of the study represents more real data, then the first (2011-2014). Cervical cancer mortality increases with age, which indicates that advanced age is a predictor factor. The age effects for almost all calendar years included in analysis (2011-2018) presented an increasing trend with age from 25 to 59, while a moderate decrease was shown within the age group from 60-64 to 65-69 and over 80 years of old. The median age of deaths from CC fluctuated inconsistently between 57 and 62 years; Interquartile range in different calendar years composed: 47-67, 52-72, and 52-67 years.

Comparatively stable median age of deaths, indicates that, there is no tendency of cervical cancer early mortality reduction. The study revealed a slight increase in CC mortality, which could be related to the improvement of death registration.

Keywords: cervical cancer, mortality, mean age.

РЕЗЮМЕ

ВРЕМЕННЫЕ ТЕНДЕНЦИИ СМЕРТНОСТИ ОТ РАКА ШЕЙКИ МАТКИ В ГРУЗИИ ЗА 2011-2018 гг.

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В Грузии рак шейки матки (РШМ) является пятым наиболее распространенным видом рака, диагностируемым после рака молочной железы, щитовидной железы, колоректального рака и рака матки. В течение с 2015 по 2018 гг. ежегодно число новых случаев рака шейки матки, зарегистрированных в регистре раковых заболеваний населения Грузии, составило 17.9, 19.6, 15.0 и 14.3 на 100 000 женщин, соответственно.

Целью исследования явилось определение смертности от рака шейки матки в Грузии за период с 2011 по 2018 гг.

Описательный анализ проведен с использованием данных о смертности за период с 2011 во 2018 гг. Национального статистического управления Грузии. В исследуемой популяции учитывали все случаи смертей, вызванных раком шейки матки (ICD 10, C53) среди женщин в возрасте от 25 лет и старше. Для оценки тенденций смертности РШМ период исследования был разделен на две группы: с 2011 по 2014 и с 2015 по 2018 гг. Для анализа данных проведена описательная статистика и оценены показатели смертности по возрастным категориям на 100 000 женского населения и другие статистические измерения - медиана, первый квартиль (Q1), третий квартиль (Q3) и межквартильный диапазон (IQR) возраста на момент смерти от РШМ. Статистический анализ выполнен с использованием программ EpiInfo v7 и Statistical Package of the Social Science (SPSS) v.23 для Windows. Для оценки статистической достоверности результатов использованы тесты статистической значимости - *p-value* и 95% доверительный интервал (95% ДИ).

Число ежегодных смертей варьирует в пределах от 121 до 185 случаев, что является колебанием смертности в пределах от 6,1 до 9,5 на 100 000 женщин. Согласно 95% ДИ разница между показателями смертности по календарным годам статистически значимой не является. Средние показатели смертности за периоды между 2011–2014 и 2015–2018 гг. составили 7.1 (ДИ=0,7) и 8,7 (ДИ=0,5), соответственно, и представляли небольшое увеличение**.** С учетом того, что в течение 2005-2010 гг. ежегодное число зарегистрированных случаев смерти от РШМ в Грузии было довольно низким и варьировало в пределах от 50 до 60, по всей вероятности, это увеличение связано с улучшением регистрации и не является достоверным ростом. Поэтому второй период исследования (2015–2018 гг.) отражает более реальные данные, чем первый (2011–2014 гг.). Влияние возраста почти на все календарные годы, включенные в анализ выявило тенденцию к увеличению заболеваемости РШМ с возрастом от 25 до 59 лет, умеренное снижение отмечено в возрастной группе 60–64 до 65–69 и старше 80 лет. Средний возраст смертности от РШМ колебался между 57 и 62 годами. Межквартильный интервал в разные календарные годы составил: 47-67, 52-72 и 52-67 годы. Сравнительно стабильный средний возраст смертных случаев указывает на то, что тенденция снижения ранней смертности от рака шейки матки не выявлена.

რეზიუმე

საშვილოსნოს ყელის კიბოს სიკვდილიანობის ტენდენციები საქართველოში, 2011-2018 წწ.

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საშვილოსნოს ყელის კიბოს ავადობის მიხედვით მეხუთე ადგილი უჭირავს საქართველოში ძუძუს, ფარისებრი ჯირკვლის, კოლორექტული და საშვილოსნოს ტანის კიბოს შემდეგ. კიბოს პოპულაციური რეგისტრის მიხედვით, საქართველოში 2015-2018 წლებში საშვილოსნოს ყელის კიბოს ავადობის მაჩვენებელმა 100000 ქალზე შეადგინა 17.9, 19.6, 15.0 და 14.3, შესაბამისად.

კვლევა მიზნად ისახავს 2011-2018 წლებში საქართველოში საშვილოსნოს ყელის კიბოს სიკვდილიანობის შეფასებას.

საქართველოს სტატისტიკის ეროვნული სამსახურის მონაცემების გამოყენებით ჩატარდა 2011-2018 წლებში საშვილოსნოს ყელის კიბოთი გამოწვეული სიკვდილიანობის აღწერილობითი ანალიზი. საკვლევ პოპულაციას შეადგენდა საშვილოსნოს ყელის კიბოთი (ICD10, C53) 25 წლის და უფროსი ასაკის ქალებში გამოწვეული ყველა გარდაცვალების შემთხვევა. სიკვდილიანობის ტენდენციების დასადგენად შესასწავლი პერიოდი დაიყო ორ ჯგუფად: 2011-2014 და 2015-2018 წლები. ჩატარდა მონაცემთა აღწერილობითი სტატისტიკური ანალიზი, შეფასდა სიკვდილიანობის და ასაკ-სპეციფიკური სიკვდილიანობის მაჩვენებლები 100000 ქალზე და სხვა სტატისტიკური პარამეტრები - გარდაცვალების ასაკის მედიანა, პირველი კვარტილი (Q1), მესამე კვარტილი (Q3) და კვარტილებს შორის ინტერვალი (IQR). სტატისტიკური ანალიზი შესრულდა EpiInfo მე-7 ვერსიის და SPSS-ის (Statistical Package of the Social Science) 23-ე ვერსიის გამოყენებით. შედეგების სტატისტიკური სანდოობის შესაფასებლად გამოყენებული იყო სტატისტიკური ტესტები - *p*-მნიშვნელობა, 95% (95%CI) სანდოობის ინტერვალი.

2011-2018 წლებში ყოველწლიურად გარდაცვლილთა რიცხვი 121–დან 185 ფარგლებში მერყეობდა, სიკვდილიანობის ცვალებადობა შეადგენდა 6.1–დან 9.5–მდე 100000 ქალზე. 95%-იანი სარწმუნობის ინტერვალის თანახმად, სიკვდილიანობის მაჩვენებლებს შორის სხვაობა კალენდარული წლების მიხედვით არ არის სტატისტიკურად მნიშვნელოვანი. სიკვდილიანობის საშუალო მაჩვენებელმა 2015-2018 წლებში 2011-2014-თან შედარებით უმნიშვნელოდ მოიმატა და შეადგინა 8.7 (SD = 0.5) და 7.1 (SD = 0.7) შესაბამისად. იმის გათვალისწინებით, რომ 2005–2010 წლებში საშვილოსნოს ყელის კიბოთი რეგისტრირებულ გარდაცვლილთა რიცხვი საქართველოში საკმაოდ დაბალი იყო - მერყეობდა 50–დან 60–მდე, სავარაუდოა, რომ ზემოაღნიშნული ზრდა უკავშირდება რეგისტრაციის გაუმჯობესებას და არ წარმოადგენს ჭეშმარიტ მატებს. კვლევის მეორე პერიოდი (2015-2018), სავარაუდოდ, ასახავს უფრო რეალურ მონაცემებს. საშვილოსნოს ყელის კიბოთი სიკვდილიანობა ასაკთან ერთად მატულობს, რაც მიუთითებს, რომ ხანდაზმული ასაკი პროგნოზული ფაქტორია. ანალიზში ჩართულ თითქმის ყველა კალენდარული წლის განმავლობაში ასაკის ზეგავლენამ აჩვენა მზარდი ტენდენცია 25-დან 59 წლის ასაკამდე, ხოლო 60-64-დან 65-69 წლამდე და 80 წელზე უფროსი ასაკის პირებში ზომიერი კლება აღინიშნა. საშვილოსნოს ყელის კიბოთი გარდაცვალების მედიანა მერყეობდა 57–დან 62 წლამდე. სხვადასხვა კალენდარულ წელს კვარტილებს შორის სხვაობამ შეადგენდა 47-67, 52-72 და 52-67 წლები, შესაბამისად.

გარდაცვალების ასაკის შედარებით სტაბილური მედიანა მიუთითებს, რომ საქართველოში საშვილოსნოს ყელის კიბოს ადრეული სიკვდილიანობის შემცირების დინამიკა არ ვლინდება. კვლევის შედეგად გამოვლენილი სიკვდილიანობის მცირედი ზრდა, სავარაუდოდ, გარდაცვალების რეგისტრაციის გაუმჯობესებას უკავშირდება.

POSITIVE EFFECT OF BETAINE-ARGININE SUPPLEMENT ON IMPROVED HYPERHOMOCYSTEINEMIA TREATMENT IN MARRIED COUPLES WITH REPRODUCTIVE DISORDERS

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Polymorphic variants of folate exchange and thus conditioned hyperhomocysteinemia (HHcy), recognized as a hereditary metabolic disorder, is a relevant factor of reproductive disorders e

For instance, the United States has shown that the fortification has given the possibility to remove genetic testing of the *MTHFR* gene variants from the clinical guidelines for the diagnostic of inherited thrombophilia and not to be carried out for patients with spontaneous abortions due to the folate status change on the population level. However, identified gene variants and moderate HHcy, as noted by clinical guidelines, in any cases, require medical genetic counseling to properly assess their impact on existing clinical symptoms. Genetic counseling should take into consideration the reason for the referral to a genetic test [12]. Some authors believe that after fortification the risk of folate-mediated diseases on the population level decreases considerably and it is impossible to determine the genetic constituent. But, genetic testing with gene-factor associations analysis would help find persons, which are at risk of developing clinical symptoms related to *MTHFR* gene variants, in order to conduct them personalized prevention measures with the consideration of the whole group B vitamins spectrum and metabolically related compounds [22].

Current precaution against folic acid (FA) "*Folic acid fortification and supplementation – good for some but not so good for others*" is the name of one of the first publications of Kim Y.I. about negative clinical effects of folic acid consumption [15], currently described [10]. Thus, the detection and personalized treatment of HHcy patients, personalized prescription optimal dose of FA in combination with other vitamins and nutrients to improve folate status and achieve stable decrease of homocysteine (Hcy) level is a conceptually new – precision medicine [3]. Timely and efficien HHcy treatment or prevention are especially necessary for patients of reproductive age to prevent undesired clinical consequences of folate-deficient conditions [4, 13].

Aim of the study was to investigate the main risk factors in the developing of HHcy in married couples with reproductive disorders and to evaluate the efficienc of short-term application of betaine-arginine supplement in treatment of identified patients

Material and methods. The studies were conducted in a total of 206 couples with reproductive disorders. 33.49% of these had natural idiopathic sterility and 66.51% had previous reproductive losses in their family history. The inclusion criteria were determined during the study planning. A couple was not included into the study if any spouse had karyotype anomalies, obesity, somatic and oncologic pathology, acute and chronic infectious diseases. Additional exclusion criteria for men were azoospermia and presence of Y-chromosome deletions. All the patients gave their informed consent to the participation in the study, provided the results of clinical, laboratory and instrumental tests, conducted prior to their being referred to medical-genetic consultation, and filled in the questionnaire, which covered their medical data and information about their lifestyle. The approval of the bioethics committee was obtained for the study. The tests for all the folate exchange indices were conducted for all the study participants: Hcy in blood plasma, FA and vitamin B12 in blood serum and polymorphism of folate exchange genes *MTHFR* (C677T, rs1801133; A1298C, rs1801131), *MTRR* (A66G, rs1801394), *MTR1* (A2756G, rs1805087), *RFC1* (G80A, rs1051266) using previously described methods [23, 24]. 116 (out of 118 detected) patients with HHcy were divided into Group 1 and Group 2. The patients in both groups were prescribed vitamins, containing 800 μg FA (in combination with 4 μg vitamin B12 average). Group 1 included 58 patients, prescribed a sachet of betaine-arginine dietary supplement - Betargin® (contains 1 g betaine, 1 g arginine and citrate ions) twice a day in addition to vitamins preparations. Group 2, also comprised of 58 patients, was prescribed vitamins preparations and not prescribed betaine-arginine containing supplement - Betargin®. Folate exchange indices (Hcy in blood plasma, FA and vitamin B12 in blood serum levels) were defined twice: before treatment and two weeks after vitamins administration.

The methods of single-factor statistical analysis were used to assess the impact of gene variants and other factors on the development of HHcy in the couples. The analysis of basic clinical characteristics and the assessment of quantitative laboratory indices involved the estimation of the mean value (M)±standard deviation (SD). The investigated indices were checked for the normality of distribution using Kolmogorov-Smirnov test. In case of normal distribution, the probability of differences in quantitative results for different groups of investigated patients was determined using Student's t-test; in case of distribution, which differed from the normal one, Mann-Whitney U-test was applied or the normalization of indices was done. Quality criteria, incidence of cases and genotype frequencies were analyzed using criteria $\chi 2$ and odds ratio (OR) within 95% of the confidence interval (CI). The differences were deemed reliable for all the types of analysis at the level of significance (p) under 0.05. The risk factors were also analyzed using the multivariate method – binary logistic regression. The calculations were done using Microsoft Excel Pro Plus 2016 and SPSS v.27 programs.

Results and discussion. The excessive Hcy level, as was proven, has unfavorable effect on the pregnancy course and associated with the birth of children with certain pathologies, impaired development, smaller weight for the gestational age. Detected differences in some results shown the presence of gene-factor interactions, when additional consumption of FA eliminated the incidence of *MTHFR* gene related pathologies on the population level. [4, 5, 12]. Regardless of this fact, the attention of researchers to HHcy has not decreased [22, 24]. 10th revision of ICD-10 (October, 2017) defined hereditary HHcy related to folate gene variants as an autosomal recessive inherited metabolic disorder (code E72.1), but it still does not have clear reference values for the Hcy level, while WHO published reference values for blood serum FA and erythrocytes FA clearly [30]. Based on existing recommendations and some studies, we considered the Hcy level in blood plasma, equal and over 12 μmol/l to be excessive in our study [19,26].

The level of Hcy in plasma, exceeding 12 μmol/l, is deemed

to be cytotoxic. The increased level of Hcy is detected among healthy population but prevails among patients with cardiovascular diseases and reproductive disorders, especially in the countries without any fortification of food products. Additional risk factors (excessive consumption of coffee, meat, unbalanced diet, smoking, alcohol consumption, etc.) increase the total HHcy risk additively and synergistically, especially in case of existing variants in folate exchange genes, thus, must be recommended plasma Hcy level under 10 μmol/l. The studies found that the levels of Hcy correlated with the indices of FA and vitamin B12 in blood serum. The sufficien level of FA in the organism of a woman prior to the pregnancy and on early stages was proven to promote the prevention of thrombophilic disorders in women and normal development of the embryo [4,26,28]. WHO defined the threshold levels of FA in blood serum: under 3 ng/ml – deficiency; 3-5.9 ng/ml – probable deficiency; 6-20 ng/ml – normal level. These threshold indices, indicated by WHO, highlight the need to control the level of folic acid in blood serum, which is first and foremost necessary for women of reproductive age, starting with the stage of planning the conception. It is believed that the optimal level of FA in blood serum prevents HHcy [30].

Our study detected HHcy in 118 (28.64%) cases (in 42 women and 76 men) among the couples with reproductive disorders, examined by us, when FA and B12 blood serum level among most was optimal (Table 1). The number of couples with the detected HHcy was 28.64% from the total number. In 18.93% of the couples, either the husband or the wife had HHcy, and in 9.71% – both husband and wife had HHcy which was conditioned by their specific diet (predominant excessive consumption of meat). Table 1 presents the results of comparison between the basic clinical and genetic charac-

Table 1. The comparison of the basic clinical and genetic characteristics in investigated groups

Characteristics		**Patients with HHcy** (≥12 μmol/l), n=118	**Patients without HHcy** (less 12 μmol/l), n=294	**Statistical differences**
Age, years		33.97±5.01	33.25±5.13	p>0.05
BMI		24.59±5.00	23.57±3.35	p>0.05
male/female, n (%)		76 (64.41%)/ 42 (35.59%)	130 (44.22%)/ 164 (55.78%)	OR=2.28 (1.47-3.55), χ^2=13.73, p=0.0002
Homocysteine, μmol/l		16.95±11.96	8.88±1.81	p<0.05
Folic acid, ng/ml		7.98±5.20	11.60±5.74	p<0.05
Vitamin B12, pg/ml		294.11±107.40	476.58±139.16	p<0.05
MTRR A66G, gene variants n (%)	66AA	29 (24.6%)	51 (17.3%)	OR=1.55 (0.93-2.60), χ^2=2.81, p=0.09
	66AG	49 (41.5%)	148 (50.3%)	OR=0.70 (0.45-1.08), χ^2=2.62, p=0.11
	66GG	40 (33.9%)	95 (32.3%)	OR=1.07 (0.68-1.69), χ^2=0.1, p=0.76
	66A	0.45	0.43	OR=0.89 (0.66-1.21), χ^2=0.55 p=0.46
	66G	0.55	0.57	
MTHFR C677T, gene variants n (%)	677CC	19 (16.1%)	161 (54.8%)	OR=0.16 (0.09-0.27), χ^2=51.16, p<0.0001
	677CT	63 (53.4%)	121 (41.2%)	OR=1.64 (1.07-2.52), χ^2=5.10, p=0.0239
	677TT	36 (30.5%)	12 (4.1%)	OR=10.32 (5.13-20.74), χ^2=57.13, p<0.0001
	677C	0.43	0.75	OR=4.08 (2.97-5.62), χ^2=79.5, p<0.0001
	677T	0.57	0.25	
MTHFR A1298C, gene variants n (%)	1298AA	76 (64.4%)	122 (41.5%)	OR=2.55 (1.64-3.97), χ^2=17.71, p<0.0001
	1298AC	38 (32.2%)	136(46.3%)	OR=0.55 (0.35-0.86), χ^2=6.82, p=0.009
	1298CC	4 (3.4%)	36 (12.2%)	OR=0.25 (0.09-0.72), χ^2=7.53, p=0.006
	1298A	0.81	0.65	OR=0.44 (0.31-0.64), χ^2=19.92, p<0.0001
	1298C	0.19	0.35	
MTR1 A2756G, gene variants n (%)	2756AA	43 (36.4%)	194 (66.0%)	OR=0.3 (0.19-0.46), χ^2=30.08, p<0.0001
	2756AG	64 (54.2%)	83 (28.2%)	OR=3.01 (1.94-4.69), χ^2=24.81, p<0,0001
	2756GG	11 (9.3%)	17 (5.8%)	OR=1.68 (0.76-3.69), χ^2=1.67, p=0.20
	2756A	0.64	0.80	OR=2.31 (1.65-3.22), χ^2=24.82, p<0.0001
	2756G	0.36	0.20	
RFC1 G80A, gene variants n (%)	80GG	20 (16.9%)	95 (32.3%)	OR=0.43 (0.25-0.73), χ^2=9.88, p=0.0017
	80GA	62 (52.5%)	132 (44.9%)	OR=1.36 (0.89-2.09), χ^2=1.97, p=0.09
	80AA	36 (30.5%)	67 (22.8%)	OR=1.49 (0.92-2.40), χ^2=2.68, p=0.10
	80G	0.43	0.55	OR=1.59 (1.17-2.15), χ^2=8.98., p=0.0027
	80A	0.57	0.45	

teristics of the examined couples depending on the detected HHcy using the methods of single-factor analysis.

Significant genetic determinant of HHcy was variants of *MTHFR*, *MTR1*, *RFC1* gene. The protective impact on HHcy development was determined for *RFC1* gene variant (80GG), but other *MTHFR*, *MTR1* gene variants increased the risk. HHcy was found significant frequently among men from the couples with reproductive disorders compared to women. Other significant factors of HHcy risk were the level of FA and B12 in serum blood at the beginning of the study, but their mean value in both groups (Table 1) located within known described threshold levels [2,6,30]. FA serum blood level was reliably lower among male patients (not shown in the Table 1) with HHcy (6.94±3.67 ng/ml) compared to females with HHcy (9.87±6.86 ng/ml).

Historically, the deficiency of vitamin B12 was determined and studied in clinical conditions, when the symptoms, caused by malignant anemia, malabsorption or severe vegan diet, were studied [1]. However, it has been determined that vitamin B12 deficiency is widely common among many groups of population and is considered to be the healthcare system problem. According to the data of different studies, the incidence of vitamin B12 deficiency is about 40 % [11]. The total concentration of vitamin B12 in blood serum or plasma is used as a biomarker of the first line of deficienc . According to WHO recommendations, the threshold value is 203 pg/ml [6]. But, there are other threshold values in the scientific literature – from 100 to 350 pg/ml, and the researchers indicate that vitamin B12 deficiency may occur even in case of its normal concentrations [2]. Our analysis found that the mean index of vitamin B12 in blood serum was within the threshold values in both investigated groups but considerably lower in patients with HHcy compared without (Table 1).

Some authors proved that the increase within the threshold values of folate status indices, namely, the levels of FA and vitamin B12 in blood serum, in the couples during IVF planning increased the live birth rate. These studies were conducted by A.J. Gaskins et al. for the population of women, residing in the country with fortification practice [8]. A similar effect was noted for men in the work of J. Hoek et al., who demonstrated the relevance of the folate status of men, and determined that both low and high pre-conception levels of folates in erythrocytes of men were associated with the delayed embryonic growth in spontaneous pregnancy [13]. The paternal status of folic acid is an impact factor for embryo programming and endometrium sensitivity [17]. The study of J. Hoek et al. demonstrated that the increased levels of FA were as harmful as the decreased ones, and considering possible epigenetic events, they may be a relevant unpredictable risk factor for the health of the progeny. In this study, such risk effect was determined only for spontaneous pregnancy, not the ones via IVF [13]. Therefore, it is an urgent task to search for the balanced personalized approach to improving folate status indices and HHcy prevention with the consideration of genetic specificitie of patients. It also requires the population-wise specificities of FA consumption and current welfare of people of reproductive age. As seen from the results of our study, HHcy in the patients under our investigation was conditioned by variants of folate exchange genes and was more remarkable for men from the couples with idiopathic sterility or spontaneous abortions. It is also known that the HHcy level is usually higher in men than women, which increases on the level of population with age [4,26].

The method of binary logistic regression was used to assess the impact of variants of the investigated genes of folate exchange on the risk of HHcy development in our patients. A reliable genetic model of risk was built with the consideration of variants C677T of *MTHFR* gene and A2756G of *MTR1* gene and had the highest predictive value – 77.2 % (Table 2).

The next analysis included gene variants, basic clinical indices, diet specificities, personal consumption of folic acid and other vitamins, determined the highest predictive value – 85.7% for the significant model of risk (Table 3), which covered variants of genes, gender, level of vitamin B12 in serum blood and additional consumption of vitamin B12 before beginning this study. Significant determinants of HHcy development were male gender, *MTHFR, MTR1* gene variants, low vitamin B12 level and its consumption. Therefore, it is important for the patients in our investigation to have optimal intake of vitamin B12 and its increasing level in blood serum during and after HHcy treatment.

Table 2. Genetic model of HHcy risk

Genes variants	Regression coefficient	p	Exp (OR) (95% CI for exp (OR))
MTHFR C677T (TT)	3,319	0,0001	27,627 (11,902-64,128)
MTHFR C677T (CT)	1,943	0,0001	6,980 (3,267-14,914)
MTR1 A2756G (AG)	0,926	0,053	2,525 (0,989-6,451)
MTR1 A2756G (GG)	-0,383	0,422	0,682 (0,268-1,735)
Constant	-1,535	0,005	0,215

Table 3. HHcy risk model (including clinical and genetics characteristics)

Characteristics	Regression coefficient	p	Exp (OR) (95% CI for exp (OR))
MTHFR C677T (TT)	3,015	0,0001	20,382 (7,3109-56,8437)
MTHFR C677T (CT)	1,667	0,0001	5,297 (2,075-13,518)
MTR1 A2756G (AG)	0,83	0,145	2,293 (0,751-6,998)
MTR1 A2756G (GG)	-0,425	0,457	0,654 (0,213-2,004)
Gender (male)	1,042	0,001	2,834 (1,498-5,365)
Vitamin B12 level	0,010	0,0001	1,010 (1,007-1,013)
Vitamin B12 ingestion	2,213	0,038	9,144 (1,128-74,092)
Constant	-5,573	0,0001	0,004

Remethylation of Hcy and its disposal occur via methyl groups, formed during metabolic transformation involving betaine or 5-methyltetrahydrofolate [20, 27]. Betaine, a choline derivative, was proved to be extremely useful in the treatment of mild HHcy. It is especially true for patients with variants of *MTHFR* gene with low functionality when the occurring deficiency of remethylation via decreasing the activity of the enzyme produces the increase in Hcy level and the decrease in the level of methionine, whose transformations are required for the synthesis of nucleotides, proteins, neurotransmitters, etc. In some clinical cases of HHcy, related to variants of *MTHFR* gene, betaine was found to be the only supplement, able to improve the Hcy level of patients; as for our patients, the leading factor of HHcy development were variants 677TT and 677CT of *MTHFR* gene [16]. It was determined for healthy people that the level of Hcy decreased reliably better in case of FA administration compared to betaine, but the stabilizing effect on Hcy level was found for betaine [27].

There have long been hypotheses that betaine-dependent remethylation is a leading way to decrease the excessive Hcy level regardless of the reason of its occurrence [14]. Some studies proved that regardless of the genetic basis and the factor of HHcy development, there is an observed decrease in betaine level in blood plasma and tissues (liver, brain, heart, etc., but not in kidneys). It was demonstrated while examining the patients and conducting experimental work with animals. The decrease in betaine was rather considerable, on average 60% below the normal value. The decrease in betaine concentration in patients with remethylation deficiencies (for instance, variants of *MTHFR* gene, deficiency of *MTR1*) is hardly a surprise as for these patients BHMT remains the only enzyme, capable of remethylating homocysteine to methionine. Moreover, for all the reasons of HHcy occurrence there may be observed increased consumption of betaine via accumulation of Hcy – substrate for enzyme BHMT. While monitoring patients with acquired HHcy, treated without betaine, it was found that the concentrations of Hcy and betaine changed towards normalization, starting with the 6th day of treatment with vitamin B12. Therefore, the application of betaine will decrease the load on Hcy remethylation via the reaction with methionine synthase, whose activity is controlled by *MTR1* gene, which in our investigation is a component of genetic and clinical-genetic models of risk and requires vitamin B12 as a reaction cofactor [27].

Considering the described interaction between remethylation pathways and the decrease in betaine concentration in blood and tissues in case of long-term HHcy, it is relevant to consider its efficienc in treating this condition with reproductive disorders. Previous studies, using animal models, proved that deficient MTHFR was accompanied with the decrease in betaine concentration in liver, thus, its application in our patients with HHcy is completely justified as the variant of *MTHFR* gene was a leading genetic risk factor for them, and both folic acid and vitamin B12 are deposited in the liver [25]. The attraction of betaine-arginine supplement for patients with HHcy and reproductive disorders is additionally enhanced due to the determined correlation between the level of betaine and homocysteine, which was observed during pregnancy and reported in the study of Silvia Ferna`ndez-Roig et al. [7]. According to this investigation, a low folate status enhanced the decrease in betaine and its correlative relationship with Hcy level during pregnancy. In addition to a similar correlative effect, another study determined long-term stabilization of Hcy level when betaine was taken, in cases of low folate status and the action of provocative factors [27].

L-arginine, presented in the composition of Betargin®, is a source of nitrogen oxide, regulating NO-synthetase via the feedback mechanism [21]. The physiological function of nitrogen oxide lies in relaxing smooth muscles of blood vessel walls, inhibiting the aggregation of platelets and their adhesion and regulating cardiovascular and genitourinary system as well as the main components of cell immunity. The formation of nitrogen oxide by immunocompetent cells ensures the protection of the organism from bacterial infections and oncologic diseases due to the participation in the regulation of apoptotic processes [18]. Nitrogen oxide impacts the activity of many enzymes and proteins, including the one of antioxidant protection, especially in conditions of disease and stress due to excessive burden, during adaptation processes and correction of metabolic shifts. First of all, the deficiency of nitrogen oxide promotes the development of endothelial dysfunction, which accompanies the development of cardiovascular diseases and reproductive disorders, thus, when L-arginine is used, the state of the vascular wall improves and the vasodilation and fibrinolytic effects develop. Similar clinical effects of L-arginine are required to decrease the toxic effect of increased Hcy on the vascular wall [29]

Group 1 and Group 2 patients with HHcy were treated for 2 weeks. Group 1 patients received betaine-arginine supplement in addition to folic acid and vitamin B12. We found no diffe - ences in homocysteine, folic acid, vitamin B12 levels of patients Group 1 and Group 2 before treatment (Fig. 1-3).

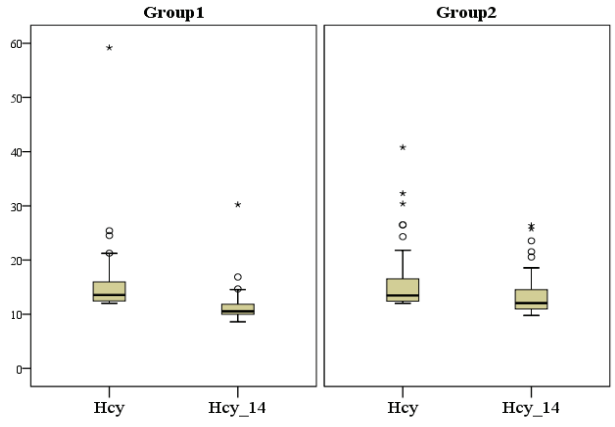

Fig. 1. Hcy (µmol/l) in patients: before (Hcy) and after treatment (Hcy_14)

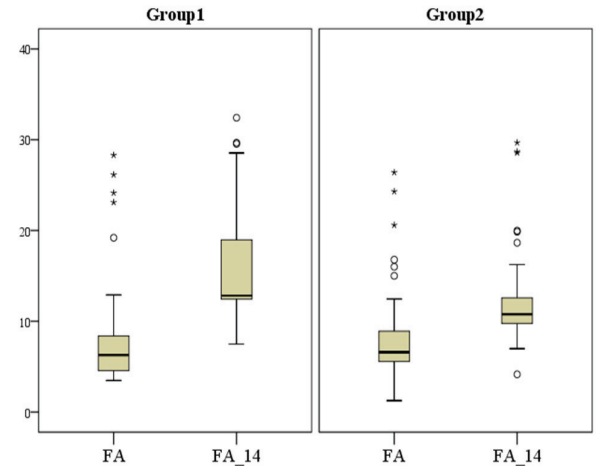

Fig. 2. FA (ng/ml) in patients: before (FA) and after treatment (FA_14)

Hcy mean values among patients Group 1 and Group 2 were 15.34±6.62 μmol/l and 15.93±5.73 μmol/l respectively, before treatment (Fig. 1), significantly decreased after treatment in both groups: 11.28±3.00 μmol/l and 13.52±3.82 μmol/l, respectively. Hcy mean values was significantly lower after treatment among patients of Group 1 compared to patients of Group 2 (Fig. 1).

FA mean values among patients of Group 1 (8.07±5.59 ng/ml) and patients of Group 2 (7.86±4.75 ng/ml) did not differ significantly at the beginning of treatment and increased significantly after the ingestion of vitamins (Fig. 2) in both groups. But patients of Group 1 (15.43±5.35 ng/ml) had significantly higher level then in Group 2 (12.21±4.82 ng/ml) after treatment.

Our analysis of B12 vitamin mean values identified the same significant rise as for FA mean values after 2 weeks of vitamins admission (Fig. 3). B12 vitamin mean values significantly increased after treatment in comparison before treatment. Also no reliable difference was in B12 vitamin mean values before vitamins consumption: Group 1 (300.95±125.69 pg/ml) and Group 2 (288.37±87.34 pg/ml) (Fig. 3), then a significantly increased indices was observed in Group 1 (542.40±137.84 pg/ml) compared to Group 2 (432.31±85.31 pg/ml) after treatment.

The patients of Group 1 with betaine-arginine supplementation had significantly lower Hcy mean values compared to patients of Group 2. The number of patients with Hcy level over 12 μmol/l significantly decreased in 47 patients from 58 (81,03%) in Group 1 against 29 patients from 58 (50%) in Group 2 (χ^2=12.36, p=0.0004).

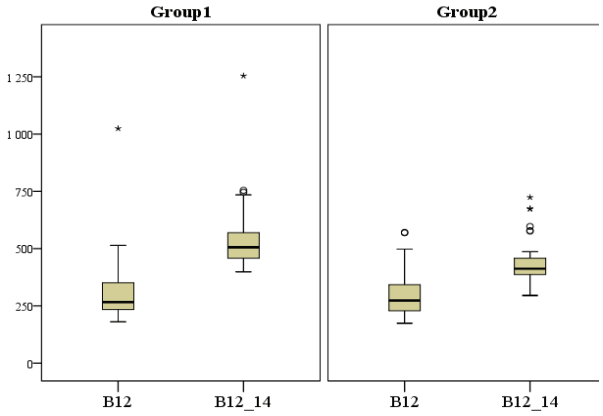

Fig. 3. Vitamin B12 (pg/ml) in patients: before (B12) and after treatment (B12_14)

Thus, the most efficien treatment was in patients group where prescribed betaine-arginine supplement in addition to FA and vitamin B12. The mentioned clinical effect indicated that the application of a betaine-arginine supplement improved the folate status of patients with reproductive disorders considerably, which is relevant in increasing the live birth rate in the family in the future.

Conclusions. The highest predictive value of hyperhomocysteinemia development in patients with reproductive disorder was identified for the risk model included *MTHFR, MTR1* gene variants, male gender, low level of vitamin B12 in blood serum and its low additional consumption. The prescription for hyperhomocysteinemia treatment in patients with reproductive disorder folic acid, vitamin B12 and betargin during two weeks significantly improved all indices (homocysteine in plasma blood, folic acid and vitamin B12 in blood serum) compared to patients without betargin consumption. Betaine-arginine supplementation provided significantly the best reduction of homocysteine level (less than 12 μmol/l in patient). The application of betaine-arginine supplement in the couples with reproductive disorders is a promising way of restoring all folate status indices quickly if variants of *MTHFR, MTR1* genes in patients are present. Further studies are required to determine the duration of betaine-arginine intake to achieve the target homocysteine level and to estimate the durability of the achieved effect

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SUMMARY

POSITIVE EFFECT OF BETAINE-ARGININE SUPPLEMENT ON IMPROVED HYPERHOMOCYSTEINEMIA TREATMENT IN MARRIED COUPLES WITH REPRODUCTIVE DISORDERS

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Treatment of hereditary hyperhomocysteinemia and the achievement of optimal folate status is necessary for persons of reproductive age in order to increase live birth rate. Patients are usually advised to take folic acid, a key nutrient in homocysteine remethylation. The results of study showed risk factors for hyperhomocysteinemia development in investigated married couples: male gender, *MTHFR, MTR1* genes variants, lower vitamin B12 blood serum and no additional intake of vitamin B12. Since *MTHFR, MTR1* genes variants affect to decrease the efficiency of homocysteine metabolic transformations, to contribute also to endothelial dysfunction in one of patients group we used betargine combined with folic acids and vitamin B12 administration. Patients group with combined administration including betargine within 2 weeks, in comparison with the group without its supplement, had significantly decreased level of homocysteine in plasma, less than 12 μmol/l (81.03% and 50% of cases, respectively). Folic acid and vitamin B12 mean values in blood serum was significantly increased in patients after two week vitamins administration including betargin. Further research is needed to establish the duration of betaine-arginine intake until the target homocysteine level will be reached, as well as to estimate the durability of clinical effect achieved after consumption.

Keywords: married couples, hyperhomocysteinemia, reproductive disorder, treatment, betargin.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ БЕТАИН-АРГИНИН СОДЕРЖАЩЕЙ ДОБАВКИ В ЛЕЧЕНИИ ГИПЕРГОМОЦИСТЕИНЕМИИ В СУПРУЖЕСКИХ ПАРАХ С РЕПРОДУКТИВНЫМИ НАРУШЕНИЯМИ

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Лечение наследственной гипергомоцистеинемии и достижение оптимального фолатного статуса необходимо лицам репродуктивного возраста с целью увеличения рождаемости. Пациентам обычно рекомендуют принимать фолиевую кислоту - ключевой нутриент для реметилирования гомоци-

стеина. Результаты исследования выявили факторы риска развития гипергомоцистеинемии в обследованных супружеских парах: мужской пол, варианты генов *MTHFR, MTR1*, пониженное содержание витамина B12 в сыворотке крови и отсутствие дополнительного употребления витамина B12. Поскольку варианты генов *MTHFR, MTR1* влияют на снижение эффективности метаболических преобразований гомоцистеина и на эндотелиальную дисфункцию, в одной из групп пациентов использовали бетаргин в сочетании с фолиевой кислотой и витамином B12. В группе пациентов с лечением, включавшим бетаргин в течение 2 недель, был значительно снижен уровень гомоцистеина в плазме крови, менее 12 мкмоль/л (81,03% случаев) в сравнении с группой без него (50% случаев). Уровни фолиевой кислоты и витамина B12 в сыворотке крови были значительно повышены у пациентов после двухнедельного приема витаминов, включая бетаргин. Необходимы дальнейшие исследования для определения продолжительности приема бетаин-аргинин содержащей добавки до достижения целевого уровня гомоцистеина, а также для оценки продолжительности клинического эффекта, достигаемого после приема.

რეზიუმე

ბეტაინ-არგინინის შემცველი დანამატის ეფექტურობა ჰიპერჰომოცისტეინემიის მკურნალობაზე რეპროდუქციული დარღვევების მქონე ცოლქმრულ წყვილებში

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მემკვიდრეობითი ჰიპერჰომოცისტეინემიის მკურნალობა და ოპტიმალური სტატუსის მიღწევა აუცილებელია შობადობის ამაღლებისათვის რეპროდუქციული ასაკის პირებში. პაციენტებს, როგორც წესი, ურჩევენ ფოლიუმის მჟავას - საკვანძო ნუტრიენტს ჰომოცისტეინის რემეთილირებისათვის. კვლევის შედეგებით გამოვლინდა ჰიპერჰომოცისტეინემიის განვითარების რისკის ფაქტორები: მამრობითი სქესი, გენების ვარიანტები *MTHFR, MTR1*, ვიტამინ B_{12}-ის დაბალი შემცველობა სისხლის შრატში და ვიტამინ B_{12}-ის დამატებითი მიღების არარსებობა. რადგანაც გენების ვარიანტები *MTHFR, MTR1* მოქმედებს ჰომოცისტეინემიის მეტაბოლური გარდაქმნების ეფექტურობასა და ენდოთელურ დისფუნქციაზე, პაციენტების ერთერთ ჯგუფში გამოყენებოდა ბეტარგინი ფოლიუმის მჟავასთან და ვიტამინ B_{12}-თან ერთად. პაციენტების ჯგუფში, ვისთანაც მკურნალობა მოიცავდა ბეტარგინს ორი კვირის განმავლობაში, სისხლის პლაზმაში ჰომოცისტეინის დონე მნიშვნელოვნად ნაკლები იყო – 12 მკმოლ/ლ-ზე ნაკლები (შემთხვევათა 81,03% და 50%, შესაბამისად), ბეტარგინის გარეშე ჯგუფთან შედარებით. ფოლიუმის მჟავას და ვიტამინ B_{12}-ის დონე სისხლის შრატში მნიშვნელოვნად მომატებული იყო პაციენტებში ვიტამინების ორკვირიანი მიღების შემდეგ, ბეტარგინის ჩათვლით. აუცილებელია შემდგომი კვლევების ჩატარება ბეტაინ-არგინინის შემცველი დანამატის მიღების ხანგრძლივობის განსაზღვრისათვის ჰომოცისტეინის სამიზნე დონის მიღწევის მიზნით, ასევე, მიღების შემდეგ მიღწეული კლინიკური ეფექტის ხანგრძლივობის შეფასებისათვის.

MODERN METHODS IN OTORHINOLARYNGOLOGY: POWERED-SHAVER ADENOIDECTOMY

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Adenoids are nasopharynx lymphoid tissues, which participate in the formation of Waldeyer's ring and they were described by Meier for the first time in 1868 [8]. Nowadays, adenoidectomy represents the most common procedure in childhood years, which is performed by resection of adenoids only, or in line with tonsillectomy and/or insertion of ventilation tubes in tympanic membranes [2]. Widespread conventional adenoidectomy was described the first time in 1885 [7]. While precise resection of adenoids along with maximum protection of the adjacent tissues of nasopharynx, complications are avoided, such as: bleeding, incomplete resection of adenoids, stenosis of Eustachian tube and in very rare cases, stenosis of nasopharynx. Incompleteness of conventional method with regard to complete and safe resection of adenoids leads to development of alternative methods, among them, adenoidectomy with shaver [3,6]. This become possible via development of endoscopic surgical instruments [1]. In our study, description of adenoidectomy with shaver is provided in line with its advantages and disadvantages.

Material and methods. 50 patients were enrolled in the prospective study, all of them underwent adenoidectomy with shaver within the period from January 2019 to June 2020 inclusive. Age range was 2-26 years old (average age-14 years old),

36 men (72%) and 14 women (28%). The patients suffered from the difficult in nasal breathing, breathing with mouth, snoring, sleep apnea, hearing loss, and recurrent sinusitis. Hypertrophy of adenoids was diagnosed by flexible fibrolaryngoscopy for nasopharynx. The head of the otorhinolaryngology department in a multi-profile clinic made adenoidectomy with shave .

Under general anesthesia, patients were intubated through orotracheal tube. The operating theater setup were the same as in the case of adenotonsilectomy, for decongestion swabs soaked with adrenaline by dilution 1:10,000 were placed in the nasal cavity. A mouth gag was inserted, choana and nasopharynx was assessed under visual examination were obtained using 0° lens optic with diameter 2.7 mm rigid endoscope (KARL STORZ GmbH & Co. Tuttlingen, Germany) 4 mm endoscope for adolescents, (Fig. 1). Special blade for adenoids was applied. The blade for adenoids is longer with window on the convex side and applied to have access at the superior wall of nasopharynx in trans-oral direction. Endoscope was inserted in a nose, but the blade for adenoids, under visual control, was placed trans-oral to nasopharynx (Fig.2). Adenoidectomy was started from the upper parts of nasopharynx by the blade movement from side to side and continued to the lower side. Due to joint operation of pump and blade for adenoids, removal of adenoids tissues as well as blood aspiration take place that enables, under visual control, to remove completely adenoids, inspect depth of wound, and avoid damage to subjacent tissues. Hemostasis was maintained by gauze balls soaked with water warmed at 45^0C temperature, in rare cases, special suction-coagulator for nasopharynx was applied (Fig 3). Mouth gag was removed from mouth cavity. Patients had postoperative care and they were discharged from hospital on the following day. All patients had to come to the clinic for a scheduled visit within 1 week after operation and then once a month during 3 months. At these visits, patients' nasopharynx was examined by flexible firbolaryngoscopy to observe postoperative process. Intraoperative parameters recording was carried out during the operational period: size of adenoids, duration of the operation, blood loss, depth of a wound, satisfaction of a surgeon and complications. Size of adenoids was assessed according to nasopharynx obstruction angle; duration of operation was calculated from insertion of mouth gag until its removal. Blood loss was estimated with the help of correlation of irrigational liquid and blood. Surgeon's satisfaction was assessed by degree of removal of adenoids tissue. Within one week after the operation, patients' conditions were evaluated based on the following parameters: neck pain and stiffness, change of speech and difficul in swallowing. Assessment of postoperative area was carried out through fibrolaryngoscop .

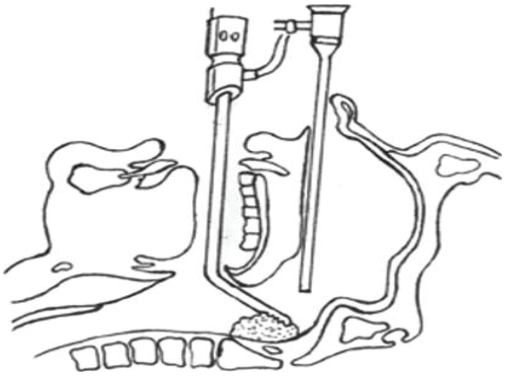

Fig. 1. Position of adenoid blade and 0 ^{0} endoscope

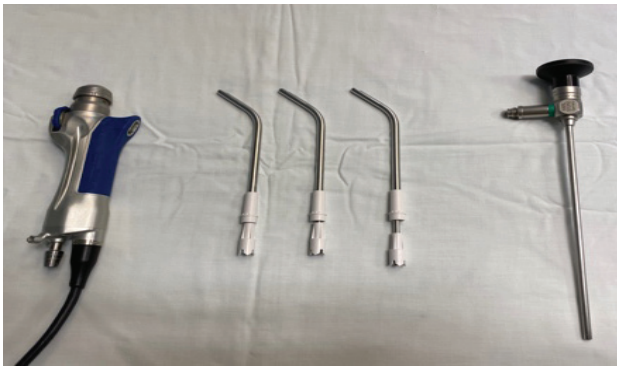

Fig. 2. Shaver, adenoid blades and 0 ^{0} endoscope

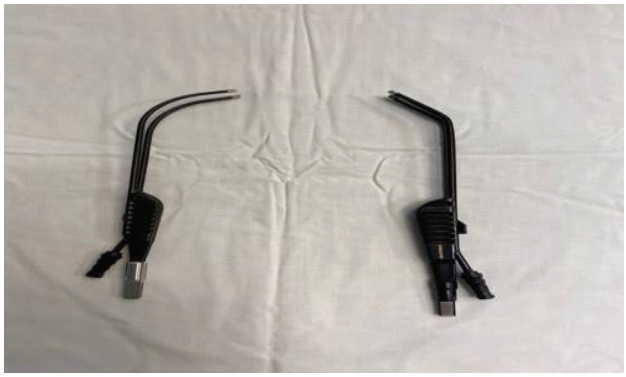

Fig. 3. Different angle suction-coagulator

Results and discussion. Indications for adenoidectomy were: impossibility of nasal breathing - 45 (90%) patients, breathing by mouth -45 (90%) v, snoring - 32 (64%) patients, otitis media - 15 (30%) patients, frequent sinusitis-7 (14%). Majority of patients had moderate or large-sized adenoids. Duration of the operation was 15 minutes on average (10-20 minutes), blood loss was 30 ml on average (24-42 ml). Adenoids were removed completely, depth of a wound was adequate, and no intraoperative complications were revealed in patients. In 5 patients (10%) on 4th day from the operation, pain and stiffness of the neck was seen that resolved by taking analgesics, namely Ibuprofen (dosing according to age). Within 10 days after the operation, all patients returned to their usual lifestyle. Within 1 year after the operation, all patients were performed endoscopy of nasal cavity. No stenosis of Eustachian tubes and nasopharynx was revealed in any patients.

Adenoidectomy represents the most common surgical inter-

vention in childhood years [4]. Although this operation is considered as a safe intervention, complications may be developed. The most frequent complication is bleeding (0.5-8% cases)[9]. Operative technique applied can have a significant impact on intraoperative bleeding, postoperative pain and recovery period, as well as formation of such complication, as stenosis of Eustachian tubes and nasopharynx, which is very rare, but difficul to resolve [1].

Traditional adenoidectomy is performed by adenotome. The main disadvantage of this method is that the operation is made without visual control, as a result of which mucous membrane of choana, bulb of Eustachian tube and nasopharynx can be damaged, as well as adenoids tissue may be left causing obstruction in the upper parts of nasopharynx [10,11]. In order to avoid these complications, alternative methods from usual adenoidectomy exist, such as, pump diathermic ablation, which is provided as a safe alternative with minimum blood loss [7], however, this alternative intervention can cause deep burn of adjacent tissues, the same can be seen with CO_2 laser, which requires taking additional safety measures [6]. The cases of stenosis of nasopharynx were revealed after adenoidectomy performed by (Potassium Titanyl Phosphate) KTP laser. Other methods include radiofrequency adenoidectomy [6] and adenoidectomy performed by electric molecular-resonance instrument [6]. Adenoidectomy with shaver is a newly described method. We, within the frame of the prospective study, reviewed patients, who underwent adenoidectomy with shaver and reveal both positive and negative sides of this intervention.

Shaver is actively used in endoscopic surgery for nasal sinuses, where preciseness is essential to avoid invasion into the orbit or cranial cavity. Adenoidectomy with shaver and transnasal endoscopic approach was performed for the first time in 1997 [3,10,11], mirrors are also used for visualization instead of endoscope [7,10].

Under Ozturk method [7] resection of tissue with shaver was complete and with appropriate depth compared to removal of tissues by adenotome. The prospective study in patients with adenoidectomy performed by traditional method showed that 39% of patients had left adenoid tissue, removal of which was carried out by shaver. [11].

Use of rigid endoscope has its advantages. With its help, full visualization of nasopharynx is possible that gives a possibility to a surgeon to remove completely adenoids without damage to adjacent tissues [7].

Use of shaver has its disadvantages, expensive equipment is required to make this operation, also adenoid blade needs to be changed after a while. In the opinion of several authors, movement of shaver head is restricted in the case, when endoscope and shaver is placed in one nostril [7,10]. Settlement of this problem is possible by trans-oral insertion of shaver. [11]. Also, taking tissue sample for histomorphological examination cannot be managed during adenoidectomy with shaver.

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SUMMARY

MODERN METHODS IN OTORHINOLARYNGOLOGY: POWERED-SHAVER ADENOIDECTOMY

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Endoscopic adenoidectomy with shaver is a safe, precise and fast procedure with minimal blood loss. With the help of this method, adenoids are completely removed without damage to adjacent tissues. Use of endoscope provides the possibility to display the operation on the screen in enlarged format and if applicable, the operation may be recorded. Controlled resection of tissues with shaver minimizes complications to the extent possible.

50 patients have been participated in the prospective study, all these patients had adenoidectomy with shaver, within the period from January 2019 to June 2020 inclusive. Age range was 2-26 years old. In order to determine efficac of the method during the operation course, attention is to be paid to the following criteria: duration of the operation, blood loss, complications, perfection, depth of wound, satisfaction of a surgeon and recovery period. Average duration of the operation accounted for 15 minutes (10-20 minutes) and average blood loss was 30ml (within the range of 24-42ml). Complete resection was made under visual control amid insignificant complications, adequate depth of wound and surgeons' high satisfaction was achieved. Adenoidectomy with shaver

is a fast, precise and safe procedure. The operation is made through full visual control, accordingly, complete resection of adenoids is carried out without damage to adjacent tissues ensuring a minimum chance for postoperative complications.

Keywords: adenoidectomy, shaver, endoscope.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ СОВРЕМЕННОЙ ТЕХНИКИ В ОТОРИНОЛАРИНГОЛОГИИ: АДЕНОИДЭКТОМИЯ С ШЕИВЕРОМ

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Эндоскопическая аденоидэктомия с шеивером является безопасной, точной и быстрой процедурой с минимальной кровопотерей. С помощью этого метода аденоиды полностью удаляются без повреждения соседних тканей. Использование эндоскопа позволяет отобразить операцию на экране в увеличенном формате и, в случае надобности, произвести запись операции. Контролируемая резекция тканей шеивером сводит к минимуму возможные осложнения.

В проспективном исследовании приняли участие 50 пациентов в возрасте 2-26 лет. Всем пациентам проведена аденоидэктомия шеивером в период с января 2019 г. по июнь 2020 г. включительно. Эффективность операции определялась следующими критериями: продолжительность, кровопотеря, осложнения, глубина раны, удовлетворенность хирурга и период восстановления. Средняя продолжительность операции составила 15 минут (10-20 минут), средняя кровопотеря - 30 мл (в диапазоне 24-42 мл). Полная резекция проведена под визуальным контролем на фоне незначительных осложнений. Аденоидэктомия с шеивером является быстрой и безопасной процедурой. Операция проводится под полным визуальным контролем, соответственно, резекция аденоидов проводится без повреждения соседних тканей, что обеспечивает минимальную вероятность возникновения послеоперационных осложнений.

რეზიუმე

თანამედროვე ტექნიკის გამოყენების ეფექტურობა ოტო-რინო-ლარინგოლოგიაში: ადენოიდექტომია შეივერით

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შ.პ.ს. ‘’ნიუ-ჰოსპიტალს’’, ოტო-რინო-ლარინგოლოგიის დეპარტამენტი, თბილისი, საქართველო

ენდოსკოპიური ადენოიდექტომია შეივერით წარმოადგენს უსაფრთხო, ზუსტ და სწრაფ პროცედურას სისხლის მინიმალური დანაკარგით. მისი საშუალებით სრულად ხდება ადენოიდების მოცილება მიმდებარე ქსოვილების დაზიანების გარეშე. ენდოსკოპის გამოყენება საშუალებას იძლევა მოხდეს ოპერაციის ეკრანზე გამოტანა გადიდებულ ფორმატში და საჭიროების შემთხვევაში ოპერაციის ჩაწერა. შეივერით ქსოვილების კონტროლირებადი რეზექცია მინიმუმამდე ამცირებს გართულებებს.

პროსპექტული კვლევაში მონაწილეობდა 50 პაციენტი, რომელთაც ჩაუტარდათ ადენოიდექტომია შეივერით, 2019 წლის იანვრიდან 2020 წლის ივნისის ჩათვლით. ასაკობრივი დიაპაზონი შეადგენდა 2-26 წელს. მეთოდის ეფექტურობის განსაზღვრისათვის ოპერაციის მსვლელობის დროს ყურადღება ექცევა შემდეგ კრიტერიუმებს: ოპერაციის ხანგრძლივობა, სისხლის დანაკარგი, გართულებები, ჭრილობის სიღრმე, ქირურგის კმაყოფილება და გამოჯანმრთელების პერიოდი. ოპერაციის საშუალო ხანგრძლივობა შეადგენდა 15 წუთს (10-20 წუთის ფარგლებში), ხოლო სისხლის დანაკარგი - საშუალოდ 30 მლ (24-42 მლ-ის ფარგლებში). სრული რეზექცია მოხდა ვიზუალური კონტროლის ქვეშ, უმნიშვნელო გართულებების ფონზე. ჭრილობის სიღრმე იყო ადეკვატური, ქირურგის კმაყოფილების მაჩვენებელი - მაღალი. ადენოიდექტომია შეივერით არის სწრაფი, ზუსტი და უსაფრთხო პროცედურა. ოპერაცია ტარდება სრული ვიზუალური კონტროლით, რის გამოც ხდება ადენოიდების სრულად მოკვეთა, მიმდებარე ქსოვილების დაზიანების გარეშე, რაც, თავის მხრივ, უზრუნველყოფს პოსტოპერაციული გართულებების მინიმიზაციას.

DENTAL STATUS FEATURES IN PATIENTS DURING ANTI-CANCER CHEMOTHERAPY (TRANSCARPATHIAN ANTITUMOR CENTER EXPERIENCE)

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One of the most common complications of complex anticancer therapy is the development of various lesions of the oral cavity, including mucositis which adversely affect the quality of life [2], limits the dose of chemotherapy and radiotherapy, and further adversely affects the effectiveness of complex therapy and increase the cost of rehabilitation. In addition, mucositis of the oral cavity significantly increases the cost of treatment of cancer patients and increases the length of hospitalization. There are a number of publications that demonstrate correlations between the level of dental health, the level of oral hygiene and the severity of secondary lesions of the maxillofacial tissues on the background of antitumor chemotherapy. Therefore, the control of dental status and oral hygiene [9] is important in predicting and preventing the development of severe mucositis [5,12].

According to officia sources of medical statistics in many countries around the world it may be judged on a consistently high number of cases of malignant tumors among the population which brings this type of pathology into a number of the most pressing health care problems. According to public health experts, the number of patients with malignant neoplasms may reach up to 1.4% of the population. WHO reports show that mortality from cancer is on the second place after diseases of the circulatory system in the structure of overall mortality so the issues of prevention, timely diagnosis, treatment of tumors, palliative care, comprehensive rehabilitation of the patient and ensuring a proper quality of life are extremely important. And the role of the dentist in such rehabilitation of the patient today is not properly assessed [8,12,14].

Modern protocols for the treatment of malignant tumors of various localizations include special chemotherapy and polychemotherapy [1,9]. Except tumor cells such medicines may cause a severe negative impact on all organs and systems of the body, and the oral cavity is affected among such patients in 100.0% of cases. That`s why we know a special nosological form – oral mucositis. Back in 1972, in USSR famous scientist AI Vorobyov proposed the another special definition - “cytostatic disease”, a polysyndromic disease caused by anti-cancer chemotherapy that has manifestations on different organ and systems, including oral mucosa lesions of varying severity [6,7,12]. A number of clinical and population studies have proven the role of dental rehabilitation to prevent the development of chemotherapy and radiational mucositis but as practice shows 100.0% of patients admitted to oncological and onco-hematological [25] hospitals have unsanitary oral cavity and extremely low level of individual oral hygiene. Therefore, it is of scientific interest to dynamically determine the dental status at the stages of anti-tumor radiational and chemotherapy and to identify the relationship between changes in dental status and changes on oral mucosa among the patients [16,21]. This is allowed to determine the purpose, objectives and methodology of this study.

Objective - to investigate the dental status of patients during anticancer chemotherapy by clinical examination and calculation of hygienic indices.

Material and methods. The study group included patients diagnosed with malignant tumors who were on the treatment of the underlying disease (the protocol included the use of chemotherapeutic anti-tumor drugs of different groups intravenously, orally and in combination with other methods of treatment). All the patients were hospitalized to Transcarpathian Antitumor Center of the Transcarpathian Regional Council in Ukraine (head – MD, DMSc, Prof. A.V. Rusyn). During the study, the oral cavity of 130 patients was examined (with their voluntary consent), during the examination the dental status was registered and complaints were recorded (by filling out the developed special questionnaire). Patients recorded the condition of the oral mucosa, caries intensivity index (caries: filled: removed), CPI index (due to Russel), Green-Vermilion index, Fedorov-Volodkina index, separately determined the presence of metal orthopedic dentures and destructed teeth, needs for dental care were also determined.

Totally, the study group consisted of 61 men and 69 women (Table 1), which were conditionally divided into 4 age subgroups – 35–44 years, 45–54 years, 55–64 years and 65–75 years (and senior).

Analysis of patients` medical data revealed that patients received specialized chemotherapeutic agents as follows: cetuximab, letrozole, capecitabine, bendamustine, bortezomib, rituximab, paclitaxel, vinorelbine, and oxaliplatin. These medicines have antineoplastic activity and they are able to non-selectively affect tissues with a rapid rate of regeneration which also includes the oral mucosa, ie, such medicines can cause mucositis, atrophic and ulcerative lesions of the oral mucosa.

Analysis of the anamnesis of patients’ lives revealed that they had malignant tumors of different localization mainly 3-4 degrees of severity and they were on anti-neoplastic chemotherapy for the first and second time (able 2).

The questionnaire for recording patients’ complaints at the dentist’s examination contained questions about the presence of patients with oral pain and maxillofacial area (its nature), the presence of irradiation, paresthetic sensations, xerostomia, swallowing disorders, opening of the mouth disorders, the appearance of angular cheilitis, changes in taste sensations, bleeding, pus from periodontal pockets, the formation of erosions and ulcers. Also, from the anamnesis of patients’ lives, information was established about the previous dental rehabilitation of the oral cavity, the frequency and number of visits to the dentist during the year, the presence of developed habits of proper oral care.

All results of the examination of patients were entered into a specially designed study card, and then copied to an electronic database where they were analyzed using descriptive statistics. All patient data were depersonalized in order to protect information that may constitute medical confidentialit , all patients prior to inclusion in the study groups gave written consent and received full information about the study.

The protocol of this study was previously presented and approved for use by the commission on bioethics of Uzhhorod National University.

Results and discussion. Studies have shown that, in general, patients with malignant tumors who were on complex antitumor treatment (chemotherapy) had a significant number of complaints related to dental nosology and maxillofacial lesions, unsatisfactory dental status, enough high need for oral rehabilitation and emergency dental care (Table 3).

Table 1. Age and sex characteristics of the observation group

35–44 years		45–54 years		55–64 years		65–75 years (and senior)	
Male	Female	Male	Female	Male	Female	Male	Female
12	10	14	16	21	25	14	18

Table 2. Distribution of the type and location of malignant tumors among the patients of the study group

Localization / type of tumors	Number of patients
Tumors of the head / neck area	17
Intestinal tumors	21
Breast tumors	27
Oncohematological diseases	25
Non-Hodgkin's lymphomas	11
Tumors of the female genital area	29
Total	130

Table 3. Frequency of individual complaints among patients receiving anticancer chemotherapy

Type of complaint	Frequency of occurrence, %		
	Male	Female	Total
Pain in the jaws	34.4	15.9	24.6
Oral mucosa pain	67.2	85.5	76.9
Oral mucosa burning	95.1	89.9	92.3
Oral mucosa paresthesia	98.4	97.1	97.7
Dryness of oral mucosa	100.0	100.0	100.0
Decrease and / or inversion of taste sensations	100.0	100.0	100.0
Occurrence of angular cheilitis	39.3	21.7	30.0
Gum bleeding	95.1	97.1	96.2
Purulent from periodontal pockets	23.0	13.0	17.7
Formation of erosions and ulcers on oral mucosa	62.3	65.2	63.9
Mouth opening disorders	18.0	20.3	19.2
Disorders of swallowing	8.2	11.6	10.0

Based on the analysis of complaints reported during the examination by a dentist, it was found that pain in the jaws generally occurred among 24.6% of patients (34.4% of men and 15.9% - among women), soreness of the oral mucosa - 76.9% of patients (67.2% of men and 85.5% of women), which suggests the rational use of topical anesthetics in this group of patients to alleviate their condition. Special attention should be paid to the complaints of patients, which can be partially attributed to the signs of damage to the sensitive nerves and receptors of oral mucosa – burning sensation, paresthesia, taste disturbances (dysgeusia).

The burning sensation of oral mucosa in the study group generally was registered among 92.3% of patients (95.1% of males and 89.9% of females). Paresthetic sensations were observed among 97.7% of patients – 98.4% of men and 97.1% of women. Dysgeusia (pathological changes of taste sensation) in the form of decreased acuity of food taste or inversion of taste sensations was observed among all patients in the study group. Also, all patients noted dryness of oral mucosa after the starting of chemotherapy which may be explained by dysfunction of saliva production and its secretion. Among 30.0% of patients (39.3% male and 21.7% female) angular cheilitis developed which also caused discomfort. Almost all patients – 96.2%, showed bleeding gums, and there was no significant difference between the sexes – 95.1% of men and 97.1% of women. Pus from periodontal pockets was found among a small number of patients – 17.7%, but among male patients it occurred almost twice as often – 23.0%, compared to 13.0% among women. The formation of erosions and ulcers of oral mucosa was observed among more than half of patients – 63.9%, without a significant difference between the sexes – 62.3% of men and 65.2% of women. Complaints of dysfunction were less frequent but their presence indicated the complications severity of the patients' chemotherapy. These were open mouth disorders which were observed among 19.2% of patients (18.0% of men and 20.0% of women) and swallowing disorders – 10.0%, by distribution – 8.2% of male patients and 11.6 % – female.

Subsequently, an index assessment of dental status in patients of the study group was performed (Table 4). The intensity of dental caries in the study group was 13.7 ± 1.0 with a slight predominance among male patients (14.5±0.77), compared with female patients – 12.8±1.06. This level may be assessed as high. The value of the communal periodontal index CPI (Russell index) in the group was 2.3±0.2, among the male patients the condition of the periodontium was worse – 2.3±0.2 than among women – 2.1±0.2. Evaluation of the Green-Vermilion hygiene index found that in general in the study group the level of oral hygiene was unsatisfactory – 2.2±0.3, it was worse among men

– 2.3±0.3, better hygiene was among women – 1,9±0.5. The index of the area of dental plaque by Fedorov-Volodkina in the study group was 2.6±0.8; among the men the average area of plaque was also higher, so the index was 2.7±1.0, in women the values were lower – 2.4±0.4. Assessment of inflammation of the marginal periodontium showed the presence of an inflamm - tory process of moderate severity among a significant number of patients – 41.4±9.8% in the general study group, 45.9±11.5% among men and 41.4±9.8% among women.

Additionally, patients noted the presence of metal dentures in the oral cavity, the presence of destroyed to the root level teeth and the need for emergency dental care (acute pain, the presence of broken denttures, acute trauma of the oral mucosa. Thus, a total of 76.2% of patients in the study group had metal dentures of various types (single crowns, welded crowns, bridges, cantilever structures) in the oral cavity. Among them, the male patients had less quantity – 67.2% and significantly more women – 84.1%. Destroyed crowns of teeth and unremoved broken teeth roots were observed among 56.9% of patients, for male patients were more common – 63.9%, abovementioned problem was presented only among 50.7% of women (Table 5). The need for emergency dental care was observed among 13.1% of patients in the study group, 14.8% of male patients and 11.6% of female patients.

Analysis of anamnestic data revealed that patients during the year before hospitalization to the specialized oncology hospital had an average of 0.8±0.4 visits to the dentist per year, women applied to dentist almost twice as often – 1.1±0.5 visits per year and men – 0.4±0.2. Patients in the study group also rarely used additional personal care products (devices) for oral care – a total of 9.2%; such devices were used by 6.6% of male and 11.6% of female patients.

The obtained results of study indicate the presence of problems with the oral cavity among 100.0% of patients receiving antineoplastic chemotherapy at specialized oncological hospital, as well as the presence of a sufficientl high need for specialized dental treatment. The high frequency of pain sensations and accordingly the violation of their quality of life indicates the need for additional nonsteroidal anti-inflammatory drugs with analgesic effect prescription and the use of topical anesthetics for oral mucosa analgesia during meals. The obtained data coincide with the results of clinical studies of a number of authors from ex-USSR and far abroad. The appearance of pain in bone tissue may be perceived as a manifestation of a more serious complication in the form of aseptic osteonecrosis of the jaws or activation of sources of chronic odontogenic infection which requires additional diagnosis and appointment to x-ray examinations [3,4,11,12,15,18,24].

The appearance of hyposalivation among patients is an indication for the recommendation of frequent irrigation of the oral cavity with antiseptic solutions, the use of artificial lysozyme to prevent secondary lesions of the oral mucosa and periodontium. Xerostomia and changes in taste sensations among patients are indications for correction of their diet during chemotherapy. Food should be processed mechanically with fewer irritating and spicy components and certain spices can be used to enhance the taste, although this issue is poorly understood nowadays. The appearance of angular cheilitis at the stage of chemotherapy requires additional examination as such a complication may occur both due to the development of dysbiosis of the oral cavity and in the presence of a decrease in the height of the bite (interalveolar distance). The occurrence of erosive and ulcerative lesions of the oral mucosa requires additional dental treatment such as keratoplastics, antiseptics and medicines for cleaning erosive surfaces from fibrin-like plaque which quickly forms in the oral cavity and causes significant discomfort to the patient [14,18,19,22,23].

The data obtained during clinical examinations among group of patients indicate unsatisfactory oral hygiene during antineoplastic chemotherapy which is according to some authors data and is a significant risk factor for secondary lesions of oral mucosa (mucositis). Patients had high hygiene indices and presence of marginal periodontitis. In the absence of prior dental sanitation (before antitumor treatment) and instruction in oral care the status of hygiene among patients with the first signs of oral mucositis can only become worsen. Moreover, in the presence of temporary immunosuppression due to the use of cytostatics the conditions for the exacerbation of chronic infection are created, so 13.1% of patients in the study group needed urgent dental care. The low level of oral sanitation, the need for dynamic

Table 4. The results of the index assessment of dental status among patients receiving chemotherapy

Indicator/index	Value		
	Male	Female	Total
Caries intensivity	14.5±0.77	12.8±1.06	13.7±1.0
CPI	2.3±0.2	2.1±0.2	2.3±0.2
Green-Vermilion	2.3±0.3	1.9±0.5	2.2±0.3
Fedorov-Volodkina	2.7±1.0	2.4±0.4	2.6±0.8
PMA,%	45.9±11.5	38.6±8.7	41.4±9.8

Table 5. Results of clinical examination and analysis of anamnestic data

	Value		
	Male	Female	Total
The presence of metal dental crowns and dentures,%	67.2	84.1	76.2
The presence of broken teeth (roots),%	63.9	50.7	56.9
The need for emergency dental care,%	14.8	11.6	13.1
Number of visits to the dentist in the previous year	0.4±0.2	1.1±0.5	0.8±0.4
Sanitation of the oral cavity before hospitalization to oncological hospital,%	0,0	0.0	0.0
The use of additional devices for personal oral hygiene,%	6.6	11.6	9.2

monitoring of the organs and tissues of the oral cavity, the need for prior hygiene training for cancer patients and the emergence of acute pain of dental origin suggest the rationality of involving dentists to the team of health care on an ongoing basic complex rehabilitation of patients with neoplasms [5,6,12,13,18].

Conclusions. A clinical examination of the oral cavity among 130 patients (61 men and 69 women) who were receiving anticancer chemotherapy in an oncology hospital revealed that such patients had poor oral hygiene and needed specialized dental treatment. Burning sensation of oral mucosa was present among 92.3% of patients, paresthesia – among 97.7%, taste disturbance and xerostomia – all patients. Among 30.0% there was angular cheilitis, among 96.2% bleeding gums, pus from periodontal pockets among – 17.7%, the formation of erosions and ulcers of oral mucosa – among 63.9%, mouth opening disorders – among 19.2 % of patients and swallowing disorders – 10.0%. The intensity of dental caries was 13.7±1.0, CPI index – 2.3±0.2, Green-Vermilion index – 2.2±0.3, Fedorov-Volodkina index – 2.6±0, 8; PMA index – 41.4±9.8%. 76.2% of patients had metal dentures, destroyed tooth crowns and unremoved roots – 56.9%. The need for emergency dental care was among 13.1% of patients in the study group. During the year before hospitalization, patients had 0.8±0.4 visits to the dentist per year, rarely used additional personal hygiene products for oral care – only 9.2%.

Data from Research Work. The work was performed in accordance with the plan of research works of the State Higher Educational Institution "Uzhgorod National University" and is a fragment of the scientific theme of the dental faculty: "Clinical-experimental substantiation of the application of modern dental technologies, expert evaluation of the quality of treatment and prevention of major dental diseases" (state registration No. 0113U003611).

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SUMMARY

DENTAL STATUS FEATURES IN PATIENTS DURING ANTI-CANCER CHEMOTHERAPY (TRANSCARPATHIAN ANTITUMOR CENTER EXPERIENCE)

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One of the most common complications of complex anticancer therapy is the development of various lesions of the oral cavity, including mucositis, which adversely affects the quality of life of the patient, limits the dose of chemotherapy and radiotherapy, and further adversely affects the effectiveness of complex therapy.

Objective - to investigate the dental status of patients who are in anticancer chemotherapy and radiotherapy through clinical examination and calculation hygienic indices.

During the study, the oral cavity was examined in 130 patients from 2015-2020, during the examination the dental status was registered and complaints were recorded. The dental status of patients on antitumor chemotherapy and radiotherapy by the method of clinical examination and calculation of hygienic indices (CSR (caries: sealed: removed), CPI index, Green Vermilion index, Fedorov-Volodkina index) was studied.

A clinical examination of the oral cavity of patients who were on anticancer therapy in a cancer hospital revealed that the patients had poor oral hygiene and needed specialized dental treatment. Burning of the oral mucosa was present in 92.3% of patients, paresthesia - in 97.7%, taste disturbance and xerostomia - in all patients. In 30.0% there was angular cheilitis, in 96.2% bleeding gums, pus from periodontal pockets in - 17.7%, the formation of ulcers of the oral mucosa - 63.9%, mouth opening disorders - in 19.2%. The need for dental care was in 13.1% of patients in the study group. During the year before hospitalization, patients had 0.8±0.4 visits to the dentist per year, rarely used additional personal hygiene products for oral care - in 9.2%.

The results indicate the presence of oral problems in 100.0% of patients receiving specialized antitumor chemotherapy and radiotherapy, as well as the presence of a sufficientl high need for specialized dental treatment.

Keywords: neoplasm, patients, treatment, oral cavity, examination, indexes.

РЕЗЮМЕ

ОСОБЕННОСТИ СТОМАТОЛОГИЧЕСКОГО СТАТУСА ПАЦИЕНТОВ ВО ВРЕМЯ ПРОТИВОРАКОВОЙ ХИМИОТЕРАПИИ (ОПЫТ ЗАКАРПАТСКОГО ПРОТИВООПУХОЛЕВОГО ЦЕНТРА)

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Одним из наиболее частых осложнений комплексной противоопухолевой терапии является развитие различных поражений полости рта, в том числе мукозитов, что отрицательно сказывается на качестве жизни пациента, ограничивает дозу химиотерапии и лучевой терапии, а в дальнейшем отрицательно влияет на эффективность комплексной терапии.

Цель исследования - изучить стоматологический статус пациентов, проходящих курс противоопухолевой химиотерапии и лучевой терапии, путем клинического осмотра и расчета гигиенических показателей.

В ходе исследования полость рта была обследована у 130 пациентов за 2015–2020 годы, в ходе обследования регистрировался стоматологический статус и фиксировались жалобы. Изучен стоматологический статус пациентов на противоопухолевой химиотерапии и лучевой терапии методом клинического обследования и расчета гигиенических показателей (CSR (кариес: пломбирование: удалено), индекс CPI, индекс Green Vermilion, индекс Федорова-Володкиной).

Клиническое обследование полости рта пациентов, которые проходили противоопухолевую терапию в онкологической больнице, показало, что пациенты не соблюдали гигиену полости рта и нуждались в специализированном стоматологическом лечении. Жжение слизистой оболочки полости рта имело место у 92,3% пациентов, парестезия – у 97,7%, нарушение вкуса и ксеростомия – у всех пациентов. Угловой хейлит – у 30,0%, кровоточивость десен – у 96,2%, гной из пародонтальных карманов – у 17,7%, образование язв слизистой оболочки полости рта - у 63,9%, нарушения открывания рта – у 19,2%. Потребность в стоматологической помощи была у 13,1% пациентов исследуемой группы. В течение года до госпитализации пациенты посещали стоматолога 0,8±0,4 в год, редко использовали дополнительные средства личной гигиены для ухода за полостью рта - в 9,2%.

Результаты свидетельствуют о наличии проблем с ротовой полостью у 100% пациентов, получающих специализированную противоопухолевую химиотерапию и лучевую терапию, а также о наличии достаточно высокой потребности в специализированном стоматологическом лечении.

რეზიუმე

პაციენტების სტომატოლოგიური სტატუსის თავისებურებები კიბოს საწინააღმდეგო ქიმიოთერაპიის დროს (ზაკარპატიეს კიბოს საწინააღმდეგო ცენტრის გამოცდილება)

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უჟგოროდის ეროვნული უნივერსიტეტი, [1]სტომატოლოგიის ფაკულტეტი; [2]მედიცინის ფაკულტეტი, უკრაინა

კიბოს საწინააღმდეგო კომპლექსური თერაპიის ერთ-ერთ გართულებას წარმოადგენს პირის ღრუს სხვადასხვა დაზიანების, მათ შორის – მუკოზიტების, განვითარება, რაც უარყოფითად აისახება პაციენტის სიცოცხლის ხარისხზე, ზღუდავს ქიმიო- და სხივური თერაპიის დოზას, მომავალში კი უარყოფითად მოქმედებს კომპლექსური თერაპიის ეფექტურობაზე.

კვლევის მიზანს წარმოადგენდა კლინიკური დათვალიერების და ჰიგიენური მაჩვენებლების გამოთვლის გზით სტომატოლოგიური სტატუსის შეფასება პაციენტებისა, რომლებიც იტარებდნენ კიბოს საწინააღმდეგო ქიმიო- და სხივური თერაპიის კურსს.

2015-2020 წწ. პერიოდში გამოკვლეულია 130 პაციენტის პირის ღრუ; კვლევის პროცესში რეგისტრირდებოდა სტომატოლოგიური სტატუსი და ფიქსირდებოდა ჩივილები. ქიმიოთერაპიის და სხივური თერაპიის კურსის ქვეშ მყოფ პაციენტებში კლინიკური კვლევის და ჰიგიენური გამოთვლების მეთოდით შესწავლილია სტომატოლოგიური სტატუსი (CSR: კარიესი, დაბჟენა, ამოღებული), ინდექსი CPI, ინდექსი Green Vermilion, ფიოდოროვა-ვოლოდკინას ინდექსი.

პირის ღრუს გამოკვლევამ პაციენტებისა, რომლებსაც კიბოს საწინააღმდეგო თერაპია უტარებოდათ ონკოლოგიურ საავადმყოფოში,აჩვენა,რომ პაციენტები არ იცავდნენ პირის ღრუს ჰიგიენას და საჭიროებდნენ სპეციალიზებულ სტომატოლოგიურ მკურნალობას. პირის ღრუს წვა აღენიშნებოდა პაციენტების 92,3%-ს, პარესთეზია – 97,7%-ს, გემოს შეგრძნების დარღვევა და ქსეროსტომია – ყველა პაციენტს,ჰეილიტი – 30%-ს, სისხლდენა ღრძილებიდან – 96,2%-ს, ჩირქი პაროდონტული ჯიბეებიდან – 17,7%-ს, წყლულები პირის ღრუს ლორწოვან გარსზე – 63,9%-ს, პირის გაღების დარღვევები – 19,2%-ს, სტომატოლოგიური დახმარება ესაჭიროებოდა გამოკვლეულ პაციენტთა 13,1%-ს; ჰოსპიტალიზაციამდე 1 წლის განმავლობაში სტომატოლოგთან ვიზიტი ჰქონდა 0,8±0,4 პაციენტს, პირის ღრუს ჰიგიენის დამატებითი საშუალებები გამოიყენებოდა იშვიათად – 9,2%-ში.

კვლევის შედეგები მიუთითებს პირის ღრუს პრობლემების არსებობის შესახებ პაციენტთა 100%-ში,რომლებიც იტარებდნენ სპეციალიზებულ კიბოს საწინააღმდეგო ქიმიო- და სხივურ თერაპიას, ასევე, სპეციალიზებული სტომატოლოგიური მკურნალობის ჩატარების მაღალი ხარისხით გამოხატულ საჭიროებაზე.

THE CORRELATION OF THE CHEMICAL COMPOSITION OF ENAMEL AND ORAL FLUID IN PATIENTS WITH A WEDGE-SHAPED DEFECT AND INTACT TEETH

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Current research works confirm a multifactorial etiology for non-carious cervical lesions (NCCLs) with the patient's individual characteristics which are responsible for varying degrees of tissue loss [1-3]. The formation of NCCLs of morphological type III (wedge shape (WS)) is associated with the wear of the hard dental tissues which reflects the cumulative effects of causal factors in the oral cavity [4,5]. The chemical theory explains WS occurrence by the demineralizing action of acids which dissolve enamel minerals [6]. The exposure to acids in combination with insufficien salivation rate leads to increased dissolution [7]. The effects of these and other interactions promote constant ion / substance exchange and reorganization within the tooth and on the surface of the tooth [8]. Saliva is one of the important mechanisms that protect against erosive wear [5]. Defective pellicle which is formed in case of the disturbance of saliva quantitative and qualitative parameters contributes to the development of pathology of the hard dental tissues [6]. The content of ions in the oral fluid (OF) affects the balance of the processes of demineralization and remineralization in the hard dental tissues, the permeability of the enamel to mineral substances [5,9,10]. Strictly defined concentrations of the chemical elements that make up the inorganic part of enamel and dentin ensure their hardness, resistance to environmental influences and the corresponding direction of biochemical transformations [11]. Thus, according to the macro- and microelement state of the hard dental tissues, their mineralization can be estimated [12].

Teeth wear varies widely from person to person emphasizing the need to identify the risk factors that explain this difference [5]. It is very important that all potential etiologic factors are identified and considered while examining the patients with NCCLs [3]. Some researchers believe that it is necessary to study the chemical composition of both dental tissues and biological fluids that wash the tooth in order to prevent demineralization processes [13]. Therefore, saliva is a perspective substance for the early detection of oral diseases [14]. If there is correlation between the indicators, OF composition it will be possible to think about enamel mineral state.

The purpose of the study is to determine OF chemical composition and mineralization level of patients with WS and clinically intact hard tissues, conduct correlation between the indicators of cervical enamel and OF.

Material and methods. The clinical and laboratory studies involved 22 patients (13 men, 9 women) without any somatic pathology (mean age 23.44+/-4.51 years). There were such criteria for their becoming the part of the groups as DMFT = 0, the absence of the diseases of periodontal tissues and oral mucosa, orthopedic and orthodontic structures in the oral cavity. Two groups were formed (11 patients each) to accomplish the assigned tasks based on the results of the clinical examination: case group– the patients with wedge-shaped defects (2.81+/-0.73) classified according to their morphology and depth [4]; control group the patients with clinically intact hard tissues. The work was performed in accordance with the principles of WMA Declaration of Helsinki "Ethical Principles for Medical Research involving Human Subjects", Order No. 690 of the Ministry of Health of Ukraine (dated September 23, 2009) and approved by Bioethics Commission of Donetsk National Medical University. Before being involved in the survey all the participants were provided with written informed consent.

The material for laboratory studies was unstimulated OF which was collected from 10 till 12 o'clock. Brushing teeth, eating, drinking, and smoking were excluded 2 hours before the beginning of the research. Previously, the oral cavity was thoroughly rinsed with distilled water twice. OF was collected into a sterile plastic test tube with a lid by spitting in the amount of 20 ml and then it was examined in the laboratory of the Depart-

ment of Chemical Metrology of Kharkov National University. Spectrometry method was applied to determine phosphate ions, ionized calcium, SO_4^{2-} (PO_4^{3-} with ammonium molybdate at λ = 340 nm, Ca^{2+} with o-cresolphthalein at λ = 570 nm, SO_4^{2-} with methylene blue at λ = 650 nm). We used the emission variant of atomic emission spectrometry to detect potassium and sodium (for K^+ λ = 766.5 nm, monochromator slit width is 0.5 nm, for Na^+ λ = 589.0 nm, monochromator slit width is 0.1 nm). Inductively coupled plasma atomic emission spectrometry (λ = 308.22 nm) was used to determine aluminum. Magnesium and zinc were defined using atomic absorption spectrometry (for Mg^{2+}: λ = 285.2 nm, amperage 5 mA, photoelectron multiplier 1.3 kV, monochromator slit width 0.1 nm, for Zn^{2+}: λ = 213.9 nm, amperage 5 mA, photomultiplier 1.3 kV, monochromator slit width 0.1 nm). Chloride ions were identified using an ELIS 131 Cl chloride selective electrode with an EVL-1 ME reference electrode connected to a pH meter. The samples for the content of K^+, Na^+ and Mg^{2+} were diluted with bidistilled water by 1000 times. The molar coefficient were calculated as the ratio of the amounts of chemical analytes in the supernatant. The level of OF mineralization potential was calculated as the ratio of the rate of salivation to the concentration of ionized calcium where values of 0.5 and higher were regarded as high intensity of mineralization, less than 0.5 – as decreased [15]. The salivation rate was determined in ml/min. according to the formula: the amount of taken OF / collection time [16].

We performed the correlation of the chemical composition of the oral fluid and the enamel of the cervical region of 22 teeth of both jaws that were removed for clinical indications (12 clinically intact, 10 with WS) in the patients aged 25-54 years. We used JSM-6490 LV focused beam electron microscope (scanning) with system of energy-dispersive X-ray microanalysis INCA Penta FETx3 (OXFORD Instruments, England). The chemical composition of 198 areas of the cervical enamel was determined as a percentage of the weight amounts of carbon, oxygen, calcium, phosphorus, sodium, magnesium, sulfur, chlorine, zinc, potassium, and aluminum [17]. Replication measurements were averaged in one sample before statistical analysis. The study was conducted at the base of Donetsk Institute of Physics and Technology of the National Academy of Sciences of Ukraine.

Statistical analysis was performed using the Statistica 12.0 computer program (3BA94C4ED07A). To check the presence of the relationship between the variables, the correlation analysis was carried out (Pearson's parametric correlation method) based on the determination of the parametric Brave-Pearson coefficien (r) with the confidence level of 95%. The reliability of obtained results was assessed using Student's T-test, the correlation between the indicators – based on Student's T-test using Z-test (Fisher's Z-test). The differences were considered statistically significant at $p \leq 0.05$. The significance of the diffe - ences between the groups was assessed basing on the analysis of variance.

Results and discussion. The comparative analysis of the content of chemical analytes in OF was carried out at the first stage (Table 1).

Since the indicators changed in opposite directions in the groups, it became possible to increase the significance of the differences by calculating their molar ratios (able 2).

Obtained results indicate the absence of significant differen - es in the content of chemical analytes and molar coefficient in OF ($p>0.05$). Mineralization of mixed saliva was significantly higher (0.93+/-0.29) in the control group than in the case group (0.57+/-0.28) by 1.64+/-0.11 times, p=0.04. This indicator was in high directly proportional correlation with the coefficien of dispersion of OF impedance and the rate of salivation in all patients ($p \leq 0.05$) [16]. High inverse correlation was found between the coeffic nt of OF impedance variance and the amount of Cl^- (r=-0.767, p=0.006) in the control group [16].

Table 1. The content of chemical analytes in OF, $\overline{X} \pm m$

Chemical analytes	Case group	Control group	p-value
K^+, mmol/l	25.20±5.60	24.60±5.20	0.378
Na^+, mmol/l	10.20±13.20	18.30±15.70	0.183
Mg^{2+},mmol/l	6.90±0,98	6.50±7.90	0.421
Ca^{2+}, mmol/l	1.00±0.50	1.10±0.60	0.757
PO_4^{3-}, mmol/l	3.80±1.30	2.70±1.30	0.125
Cl^-, mmol/l	21.70±6.50	19.20±5.80	0.461
$S0_4^{2-}$, mmol/l	0.0010±0,0010	0.0008±0.0011	0.207
Zn^{2+}, mg/l	0.03±0.01	0.04±0.02	0.464
Al^{3+}, mg/l	0.0003±0,0001	0,003±0,0001	0.802

Table 2. Molar ratios of chemical analytes in OF, $\overline{X} \pm m$

Molar coefficients	Case group	Control group	p-value
Na^+/K^+	0.43±0.52	0.75±0.62	0.437
Na^+/Mg^{2+}	4.83±4.86	9.44±10.06	0.183
Ca^{2+}/PO_4^{3-}	0.30±0.10	0.45±0.29	0.137
PO_4^{3-}/Ca^{2+}	4.52±3.41	3.09±1.76	0.115
Ca^{2+}/Mg^{2+}	0.58±0.46	0.85±0.97	0.344
Ca^{2+}/Cl^-	0.05±0.02	0.06±0.03	0.757
Al^{3+}/Zn^{2+}	0.0010±0.0003	0.009±0.006	0.629
Mg^{2+}/Ca^{2+}	6.87±7.00	9.71±17.00	0.399
Mg^{2+}/PO_4^{3-}	1.82±2.29	3.43±5.72	0.518

Table 3. Molar ratios of chemical analytes in cervical enamel, $\overline{X}\pm m$

Molar coefficients	Case group	Control group	p-value
Na/K	40,3956±42,1166	38,2085±41,7515	0,815
Na/Mg	11,5512±26,6174	8,8071±17,5403	0,583
Ca/P	2,5584±1,2791	1,8983±0,1864	0,005*
P/Ca	0,4565±0,1415	0,5313±0,0473	0,005*
Ca/Mg	414,5617±674,0558	361,8856±201,7616	0,672
Ca/Cl	141,7328±183,982	76,8978±22,7115	0,054
Al/Zn	36,1473±48,6261	19,8389±40,4231	0,114
Mg/Ca	0,0049±0,0040	0,0232±0,0015	0,028*
Mg/P	0,0098±0,0077	0,0060±0,0026	0,009*
K/Na	5,2881±22,3472	0,0911±0,0982	0,200

** $p \leq 0.05$*

Table 4. The correlation between the content of chemical analytes in OF and cervical enamel, r ($p < 0.0001$)

Chemical analytes	group	K^+	group	PO_4^{3-}	group	Cl^-
Ca^{2+}	I	-0.7500	I	0.5511	I	-0.7302
	II	-0.9433	II	0.9781	II	-0.9125
Na^+	I	0.5444	-		-	
	II	0.7168				
Mg^{2+}	I	0.6040	-		I	0.5684
	II	0.6570			II	0.5554
PO_4^{3-}	I	-0.8596	-		I	-0.8609
	II	-0.9545			II	-0.9110
K^+	-		-		I	0.9230
					II	0.9388

I - case group, II – control group

Table 5. The correlation between the content of molar coefficients in OF and cervical enamel, r ($p < 0.0001$)

Molar coefficients	group	Ca^{2+}/PO_4^{3-}	group	Mg^{2+}/Ca^{2+}	group	PO_4^{3-}/Ca^{2+}
Na^+/K^+	I	0.5200	-		-	
	II	0.5828				
Ca^{2+}/Mg^{2+}	I	0.8089	-		-	
	II	0.7499				
Ca^{2+}/Cl^-	I	0.6132	-		I	-0.5556
	II	0.9067			II	-0.6958
Mg^{2+}/PO_4^{3-}	-		I	0.9537	-	
			II	0.6366		

I - case group, II – control group

The data on the chemical composition of the cervical enamel of teeth with WS and intact hard tissues are presented in previous works [17]. In the samples with WS there was determined a greater amount of magnesium by 1.55 times, aluminum – by 4 times, sulfur – by 2 times, calcium by 14% [17]. Inversely proportional correlation was revealed in the cervical region of the samples of the case and control groups: high between carbon and oxygen (r=-0.7844), carbon and phosphorus (r=-0.7998), oxygen and calcium (r=-0.9069), moderate between carbon and sodium (r=-0.5265), p<0.0001. Directly proportional correlation of average strength was determined between: oxygen and sodium (r=0.5091), oxygen and phosphorus (r=0.6366), p<0.0001 The results of calculating their molar coefficient by groups are presented in Table 3.

There were the following indicators of molar coefficient in the group of the samples with WS: Mg/P – by 1.63 times higher, Ca/P by 24% higher, Mg/Ca by 4.7 times lower, P/Ca by14% lower at comparison with clinically intact samples. There was determined the following directly proportional correlation: very high between Mg/P and Mg/Ca (r=0.9597), moderate between K/Na and Ca/P (r=0.6155) p<0.0001.

The correlation analysis was performed to check the presence of the relationship between the chemical composition of OF and cervical enamel at the second stage of the study. The results of the revealed correlation between the indicators of moderate and high strength are shown in Table 4.

The distinctive feature of the relationships of the control group was the presence of moderate directly proportional correlation:

Na^+ with Cl^- (r=0.6926) and Mg^{2+} (r=0.6463), inverse proportional one: Na^+ with Ca^{2+} (r=-0,6799) and PO_4^{3-} (r=-0.6601), Mg^{2+} with Ca^{2+} (r=-0,5757) and PO_4^{3-} (r=-0.5975), p<0.0001.

The results of the revealed correlation between the indicators of molar coeffici ts of moderate and high strength are given in Table 5.

The correlation of molar coefficient of the control group distinguished itself with the presence of high and moderate strength: directly proportional – between Ca^{2+}/Cl^- and Na^+/K^+ (r=0.5117), Ca^{2+}/Mg^{2+} (r=0.7187), Mg^{2+}/Ca^{2+} and PO_4^{3-}/Ca^{2+} (r=0.7055), inversely proportional – between Ca^{2+}/Mg^{2+} and PO_4^{3-}/Ca^{2+}(r=-0.5973), p<0.0001.

Successful prevention and treatment of NCCLs requires the understanding of the risk factors and how these factors change in individual patients over time [2]. Previous studies have shown a significant relationship between tooth wear and OF physical properties [5,16]. The changes in OF physicochemical parameters are associated with the disturbance of mineralization processes which is determined by its saliva mineralization potential[16,18]. The salivary mineralization level in individuals with NCCLs was higher than 0.5 which is probably due to the increase in the amount of inorganic phosphate that is the factor that enhances OF remineralizing property [16,19]. The mineralization potential, value of the dispersion coefficien and the steepness of the dispersion of OF electrical impedance in the patients with WS were significant y lower than in the control group that is regarded as the decrease in its micellarity and mineralizing capacity [16].

As a result of the study, no significant differences have been found in the chemical composition of mixed saliva of the persons with WS and clinically intact dental hard tissues. Other authors have not found any difference in calcium and phosphorus content in OF patients with and without NCCLs either [20].

Taking into account the inter-element synergism and antagonism as well as the complex interaction at the level of a living organism of individual microelements, a more sensitive indicator of their relationship is the correlation between the ratios of certain element pairs. The imbalance in OF chemical composition led to the decrease of important calcium-phosphorus coefficien in the metabolic ratio [15]. It was significantly lower in the patients with WS. Probably it explains the lower indices of Na/K in the main group. The dynamics of the Na/K coefficien provides the information on the activity of the sympathetic-adrenal system and the state of the thyroid gland [21]. Many researchers confirm the role of endocrine pathology in the occurrence of NCCLs [6,20]. Aluminum, which was significantly higher in the cervical enamel of WS teeth, is able to influence thyroid function [22]

More calcium and phosphorus were detected ($p\leq0.05$) in the cervical enamel of teeth with NCCLs while there was a tendency towards the increase in the amount of magnesium ($p>0.05$) [17]. According to some authors' view the increase in the content of calcium and magnesium in samples with WS is a protective reaction aimed at activating the process of mineralization (remineralization) of enamel [10]. The amount of magnesium correlates with the amount of calcium, since magnesium is a physiological calcium antagonist and is important in phosphorus-calcium metabolism [11,21,23]. The 4-time increase in the aluminum content in the surface enamel of the teeth with WS confirms other researchers' opinion about its role in the pathogenesis of NCCLs [24]. And the accumulation of it by the hard dental tissues is not important so much as the disturbance of the mineral metabolism characterized by the change in the metabolism of calcium and phosphorus [24].

As may be supposed, only the outer enamel layer is prone to mineralization/demineralization[11]. It only explains the determination of the correlation of the chemical composition of enamel of the teeth surface and OF. The revealed high level of directly proportional correlation between Ca^{2+}/Mg^{2+} and Ca^{2+}/PO_4^{3-} in cervical enamel and OF makes it possible to use the Ca^{2+}/Mg^{2+} molar coefficien as an alternative indicator of enamel mineralization.

Conclusions. Apparently, there are significant individual differences in the composition and properties of OF that are responsible for the onset and progression of tooth wear and which are correlated with the chemical composition of the surface layer of enamel and they may be the risk factors for the occurrence of NCCLs. The non-invasiveness of the mixed saliva research method makes it possible to include it in individual preclinical diagnostics.

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SUMMARY

THE CORRELATION OF THE CHEMICAL COMPOSITION OF ENAMEL AND ORAL FLUID IN PATIENTS WITH A WEDGE-SHAPED DEFECT AND INTACT TEETH

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Aim - to determine oral fluid chemical composition and mineralization level in patients with a wedge-shaped defect and intact hard tissues, conduct correlation between the indicators of cervical enamel and oral fluid

We determined Ca^{2+}, PO_4^{3-}, SO_4^{2} using spectrophotometric method, Na^{+}, K^{+}, Al^{3+} by atomic emission spectrometry, Mg^{2+}, Zn^{2+} by atomic absorption spectrometry, Cl^{-} using chloride-selective electrode of pH-meter in oral fluid of 22 patients divided into two groups: case – with wedge-shaped defects (2.81+/-0.73); control – with intact teeth. Correlation of oral fluid and cervical enamel chemical composition of 22 extracted teeth (12 – intact teeth, 10 wedge shape) was made. We used JSM-6490 LV focused beam electron microscope (scanning) with system of energy-dispersive X-ray microanalysis INCA Penta FETx3.

Significant differences haven't been found in chemical analyte content and molar ratios ($p>0.05$) in oral fluid. The level of mineralization potential was 1.64+/-0.11 times higher in patients of the control group ($p\leq0.05$). The values of molar coefficient in teeth enamel with a wedge-shaped defect were high: Mg/P by 1.63 times, Ca/P by 24%, they were low: Mg/Ca – by 4.7 times, P/Ca – by 14% ($p\leq0.05$). The difference in correlation between the chemical composition of oral fluid and enamel of patients in the control group was the presence of an average directly proportional bond strength: Na^{+} with Cl^{-} and Mg^{2+}, inversely proportional: Na^{+} with Ca^{2+} and PO_4^{3-}, $p<0.0001$. Correlation between molar coefficient of oral fluid and enamel in the control group was distinguished by the presence of high and moderate correlation: directly proportional – between Ca^{2+}/Cl^{-} and Na^{+}/K^{+}, Ca^{2+}/Mg^{2+}; Mg^{2+}/Ca^{2+} and PO_4^{3-}/Ca^{2+}, inversely proportional – between Ca^{2+}/Mg^{2+} and PO_4^{3-}/Ca^{2+}, $p<0.0001$.

We have revealed correlations of the chemical composition of enamel and oral fluid which can be used to assess the mineral state of tooth enamel and control the effectiveness of prevention of the initial forms of wedge-shaped defects in terms of mixed saliva in dynamics.

Keywords: tooth wear, non-carious cervical lesions, saliva, spectrometry, analytical chemistry, scanning electron microscope.

РЕЗЮМЕ

КОРРЕЛЯЦИОННАЯ СВЯЗЬ ХИМИЧЕСКОГО СОСТАВА ЭМАЛИ И РОТОВОЙ ЖИДКОСТИ У ПАЦИЕНТОВ С КЛИНОВИДНЫМ ДЕФЕКТОМ И ИНТАКТНЫМИ ЗУБАМИ

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Цель исследования - определить химический состав и уровень минерализации ротовой жидкости у пациентов с клиновидным дефектом и интактными твердыми тканями, определить корреляционную связь между показателями пришеечной эмали и ротовой жидкости.

Составлены две группы: основная – 10 удалённых зубов с клиновидными дефектами (2.81±0.73); контрольная – 12 интактных зубов. В ротовой жидкости у 22 пациентов определены: Ca^{2+}, PO_4^{3-}, SO_4^{2} - спектрофотометрическим методом, Na^{+}, K^{+}, Al^{3+} – методом атомно-эмиссионной спектрометрии, Mg^{2+}, Zn^{2+} – методом атомно-абсорбционной спектрометрии, Cl^{-} с использованием хлоридселективного элетрода - pH-метра; их соотношение, минерализационный потенциал. Определена корреляция химического состава ротовой жидкости и пришеечной эмали 22 удаленных зубов (12 – интактных, 10 - с клиновидным дефектом). Использовали растровый (сканирующий) электронный микроскоп JSM 6490 LV с системой энергодисперсионного рентгеновского

анализа INCA Penta FETx3 (OXFORD Instruments, England).

Достоверных различий в содержании химических аналитов и их молярных соотношениях в ротовой жидкости не выявлено ($p>0.05$). Уровень минерализационного потенциала в 1,64±0,11 раза выше у пациентов контрольной группы ($p\leq0.05$). Значения молярных коэффициентов в эмали зубов с клиновидным дефектом были выше: Mg/P - в 1,63 раза, Ca/P - на 24%, меньше: Mg/Ca – в 4,7 раза, P/Ca – на 14% ($p\leq0.05$).

Разница в корреляции между химическим составом ротовой жидкости и эмали пациентов контрольной группы заключалась в наличии средней силы связи прямо пропорциональной: Na^+ с Cl^- и Mg^{2+}, обратно пропорциональной: Na^+ с Ca^{2+} и PO_4^{3-}, Mg^{2+} с Ca^{2+} и PO_4^{3-} ($p<0.0001$). Корреляция молярных коэффициентов ротовой жидкости и эмали в контрольной группе отличалась присутствием высокой и средней связи: прямопропорциональной – между Ca^{2+}/Cl^- и Na^+/K^+, Ca^{2+}/Mg^{2+}; Mg^{2+}/Ca^{2+} и PO_4^{3-}/Ca^{2+}, обратнопропорциональной – между Ca^{2+}/Mg^{2+} и PO_4^{3-}/Ca^{2+}, $p<0.0001$.

Выявлены корреляционные взаимосвязи химического состава эмали и ротовой жидкости, которые могут быть использован для оценки минерального состояния эмали зубов и контроля эффективности профилактики начальных форм клиновидных дефектов по показателям смешанной слюны в динамике.

რეზიუმე

კორელაცია მინანქრისა და და პირის ღრუს სითხის შემადგენლობას შორის პაციენტებში სოლისებური დეფექტით და ინტაქტური კბილებით

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კვლევის მიზანს წარმოადგენდა პირის ღრუს სითხის ქიმიური შემადგენლობის და მინერალიზაციის ხარისხის განსაზღვრა პაციენტებში სოლისებური დეფექტით და კბილების ინტაქტური მაგარი ქსოვილებით, ასევე, კორელაციური კავშირის დადგენა კბილის ყელის მიმდებარე მინანქრისა და პირის ღრუს სითხის მაჩვენებლებს შორის.

კვლევისათვის ფორმირებული იქნა ორი ჯგუფი: ძირითადი – 10 ამოღებული კბილი სოლისებური დეფექტებით (2.81±0.73), საკონტროლო - 12 ინტაქტური კბილი. 22 პაციენტის პირის ღრუს სითხეში განსაზღვრულ იქნა: Ca^{2+}, PO_4^{3-}, SO_4^{2} – სპექტროფოტომეტრიული მეთოდით, Na^+, K^+, Al^{3+} – ატომურ-ემისიური სპექტრომეტრიის მეთოდით, Mg^{2+}, Zn^{2+} – ატომურ-აბსორბციული სპექტრომეტრიის მეთოდით, Cl^- - ქლორიდსელექციური ელექტროდის - pH-მეტრის გამოყენებით, მათი თანაფარდობა, მინერალიზაციური პოტენციალი. 22 ამოღებულ კბილში (12 – ინტაქტური, 10 – საკონტროლო) განსაზღვრულია კორელაცია პირის ღრუს სითხისა და ყელის მიმდებარე მინანქრის ქიმიურ შემადგენლობას შორის. გამოყენებულია მასკანირებელი ელექტრონული მიკროსკოპი JSM-6490 LV ენერგოდისპერსიული რენტგენული ანალიზის სისტემით X-INCA Penta FETx3 ((OXFORD Instruments, England).

სარწმუნო განსხვავება ქიმიური კომპონენტების შემცველობასა და მათი მოლარობის თანაფარდობას შორის პირის ღრუს სითხეში აღმოჩენილი არ იქნა ($p>0.05$). მინერალიზაციური პოტენციალი 1,64±0,11-ჯერ უფრო მაღალია საკონტროლო ჯგუფის პაციენტებში ($p\leq0.05$). მოლარობის კოეფიციენტების მნიშვნელობა სოლისებური დეფექტის მქონე კბილების მინანქარში იყო: მაღალი - Mg/P - 1,63-ჯერ, Ca/P - 24%-ით, დაბალი - Mg/Ca – 4,7-ჯერ, P/Ca – 14%-ით ($p\leq0.05$).

სხვაობა კორელაციაში პირის ღრუს სითხისა და მინანქრის ქიმიურ შემადგენლობას შორის საკონტროლო ჯგუფის პაციენტებში გამოიხატებოდა: საშუალო პირდაპირპროპორციულ დამოკიდებულებაში - Na^+-ისა Cl^--თან და Mg^{2+}-თან, უკუპროპორციულ დამოკიდებულებაში - Na^+-ისა Ca^{2+}-თან და PO_4^{3-}-თან, Mg^{2+}-ისა Ca^{2+}-თან და PO_4^{3-}-თან ($p<0.0001$). პირის ღრუს სითხის და მინანქრის მოლარობის კოეფიციენტების კორელაცია საკონტროლო ჯგუფში გამოირჩეოდა მაღალი და საშუალო კავშირების არსებობით: პირდაპირპროპორციულისა - Ca^{2+}/Cl^- და Na^+/K^+, Ca^{2+}/Mg^{2+}; Mg^{2+}/Ca^{2+} და PO_4^{3-}/Ca^{2+}, უკუპროპორციულისა - Ca^{2+}/Mg^{2+} და PO_4^{3-}/Ca^{2+}, $p<0.0001$.

გამოვლენილია მინანქრის და პირის ღრუს სითხის ქიმიური შემადგენლობის კორელაციური კავშირები, რაც შეიძლება გამოყენებულ იქნას კბილების მინანქრის მინერალური მდგომარეობის შეფასებისა და სოლისებური დეფექტების ადრეული ფორმების პროფილაქტიკისათვის შერეული ნერწყვის მაჩვენებლების მიხედვით დინამიკაში.

CARDIOVASCULAR EVENT ASSESSMENT IN PATIENTS WITH NONOBSTRUCTIVE CORONARY ARTERY DISEASE UNDERGOING DUAL ANTIPLATELET TREATMENT

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Nonobstructive coronary artery disease (NObCAD) is atherosclerotic plaque that would not be expected to obstruct blood flow or result in anginal symptoms. Although such lesions are relatively common, occurring in 10% to 25% of patients undergoing coronary angiography [1,2].

Nonobstructive coronary artery disease has historically been considered benign and clinically insignificant, however it was associated with a 28 to 44 percent increased risk of a major cardiac event such as a heart attack or death, in a new study presented at the American Heart Association's Quality of Care and Outcomes Research 2014 Scientific Sessions

Nonobstructive CAD in acute coronary syndromes (ACS) has attracted much attention because of the relatively high incidence of adverse cardiovascular events if not appropriately diagnosed and treated [3,4].

Dual antiplatelet therapy (DAPT) consisting of aspirin and a $P2Y_{12}$ receptor antagonist is a fundamental component of acute coronary syndrome (ACS) management. However, DAPT of NObCAD remains a major topic of discussion and is of particular importance.

The aim of our study was to learn the differences in baseline presentation between NObCAD and obstructive coronary artery disease (ObCAD) subjects, to compare the likelihood of several clinical outcomes and the rate of primary endpoints between this groups.

Material and methods. Out study included 165 patients: 115 patients with NObCAD ACS, 50 – with ObCAD ACS. Inclusion criteria: age >18 year; Presence of any atherosclerotic stenosis greater than 20% but less than 50% in the left main coronary artery, and greater than 20% but less than 70% in any other major epicardial coronary artery. Exclusion criteria: Age<18 year; Antiplatelet treatment in past; Coronary revascularization in past; Absolute contraindications for antiplatelet treatment; After providing written informed consent, patients with NObCAD ACS were randomly assign in an 1:1 ratio in 2 group: Group A (n=55) received dual antiplatelet treatment with aspirin 100-160 mg once daily and clopidogrel 75 mg once daily for three months. Group B (n=60) received only aspirin 100-160 mg once daily for three months. 50 patients with ObCAD ACS entered in group C – controlled group, patients were treated according appropriate treatment guidelines.

Clinical, demographic and treatment data were investigated. Demographic variables included age and gender. Comorbidities included smoking, diabetes, hyperlipidemia, hypertension, obesity, and prior history of heart disease (angina, heart failure, myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention), renal and liver disease. ECG changes and initial laboratory data were recorded. Laboratory analyses: CBC, urine test, serum lipid profile, fasting blood glucose and HbA_1C, creatinine and eGFR, liver enzymes were provided. All patients underwent coronary angiography. Data describing patient management included use of β-blockers, aspirin, ACE inhibitors or angiotensin receptor blockers, lipid-lowering agents.

We categorized each patient by CAD extent. To accomplish this, we categorized each patient by CAD severity in a single, double, or triple-vessel distribution: 1-, 2-, and 3-vessel nonobstructive CAD; and 1-, 2-, and 3-vessel obstructive CAD. Rates of MI, all-cause mortality, and the combined outcome during the full study period were calculated and compared by CAD extent.

Follow-up evaluations were performed at one, two and three months and 1 year. At these visits was assessed primary endpoints - MACE (Major adverse cardiac events): 1year hospitalization for Myocardial infarction or other cardiovascular causes after index angiography, cardiovascular death, revascularization, survival. We studied type and frequency of bleeding during treatment and follow up period. Severe bleeding was defined as fatal or intracranial hemorrhage, or bleeding cause hemodynamic compromise; moderate bleeding was defined as bleeding requiring transfusion not characterized as severe and mild asymptomatic bleeding.

All the analysis was calculated using the Statistical Package for Social Sciences (SPSS, version 22) software. A Student's t-test was used to compare the differ nce in the continuous variables between groups. A value of $p<0.05$ was considered to be statistically significant.

Results and discussion. Baseline characteristics of patients are displayed in Table 1.

NObCAD patients (group A and B), as compared to ObCAD subjects (group C) had less cardiovascular risk factors at baseline (including diabetes mellitus, hypertension, dyslipidemia, cigarette smoking).

As shows the analysis of data, after one year from an initiation of treatment, frequency of CVD in group A is 29.1%, in group B – 35% and in group C - 64%, and events frequency increased with CAD extension. Hospitalization for MI was significantly higher in group C: 16.4% in group A, 18.3% - in group B and 24% in group C. Revascularization rate was 10.9% in group A, 20% – in group B and 38% in group C. Cardiovascular death rate was significantly higher in group C. There were no significant difference between all 3 groups according bleeding frequency. All cases of bleeding was mild and asymptomatic.

Despite the prevalence of nonobstructive CAD identified by coronary angiography, little is known about its risk of adverse outcomes. More data on nonobstructive CAD patients and their longitudinal outcomes are essential for understanding their risks for adverse cardiac outcomes and potential therapeutic implications [5,6]. Differences in prognosis and baseline clinical presentation have been documented among patient with acute coronary syndrome and coronary artery disease with obstructive (ObCAD) or nonobstructive arteries (NObCAD), but the rates of events largely varied across single studies.

An unstable coronary plaque is the primary cause of the coronary syndrome. Thrombus formation occurs under conditions of high shear stress and is principally driven by platelet aggregation in acute coronary syndrome. Platelet aggregation during intracoronary thrombus represents the dramatic effects that antiplatelet therapies have on clinical outcomes [7].

Despite evidence of myocardial ischemia that is demonstrated after presenting with cardiac symptoms, an angiogram that shows nonobstructive CAD will ultimately result in little medical treatment. This approach is of concern to clinicians because many of these patients will continue to have symptoms that will lead to rehospitalization, repeated diagnostic testing [8].

Table 1. Clinical characteristics of patients

Variables	Group A (n=55)	Group B (n=60)	Group C (n=50)
Age, mean	58.2±8.9	61.3±9.02	63.2±7.4
Female %	38 (69.1%)	35 (58.3%)	21(42%)
Smoker %	19(34.5%)	15 (25%)	21(42%)
Hypertension %	35 (63.6%)	35 (58.3%)	41 (82%)
Diabetes Mellitus %	9 (16.4%)	11 (18.3%)	17(34%)
Heart Failure	11(20%)	15(25%)	11(22%)
History of atrial fibrillation	5(9.1%)	4(6.7%)	5(10%)
History of stroke %	3(5.5%)	2(3.3%)	0
COPD %	0	2(3.3%)	2(4%)
Dyslipidemia %	29(52.7%)	33(55%)	37 (74%)
Chronic renal disease %	4(7.3%)	3 (5%)	3(6%)
Liver disease %	0	0	2(4%)
CAD extend	1 vessel – 26(47.3%) 2 vessel - 11(20%) 3 vessel – 18 (32.7%)	1 vessel - 36 (60%) 2 vessel-13(21.6%) 3 vessel–11 (18.3%)	1 vessel - 9 (18%) 2 vessel - 21(42%) 3 vessel – 20 (40%)

Table 2. Clinical outcomes, adverse events and primary end points assessment

End points	Group A (n=55)			Group B (n=60)			Group C (n=50)		
CAD extend	1 vessel	2	3	1	2	3	1	2	3
CVD events	2 (3.6%)	5 (9.1%)	9* (16.4%)	4* (6.7%)	7* (11.7%)	10* (16.7%)	3 (6%)	11* (22%)	18* (36%)
Hospitalization for MI	2 (3.6%)	2 (3.6%)	5 (9.1%)	2 (3.3%)	4 (6.6%)	5 (8.3%)	2 (4%)	3 (6%)	7* (14%)
Revascularization	0	1 (1.8%)	5* (9.1%)	1 (1.7%)	4* (6.6%)	7* (11.7%)	2* (4%)	12* (24%)	15* (30%)
Cardiovascular death	0	0	0	0	1 (1.7%)	2 (3.3%)	1 (2%)	3 (6%)	2 (4%)
Bleeding	2(3.6%)		1(1.8%)		1(1.7%)	1(17%)	1(2%)		1(2%)

** - P<0.05*

The effect of dual antiplatelet therapy following an acute coronary syndrome was confirmed by the trials. Combined aspirin and clopidogrel therapy decreased the 1-year incidence of cardiovascular events by up to 20% compared with aspirin alone. Although a large volume of evidence supporting the use of dual antiplatelet therapy in patients with the acute coronary syndrome, there remains major uncertainty regarding the treatment of patients with NObCAD.

After data assessment we can tell, that the combination of clopidogrel and aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, but there was significant difference between groups regarding the CVD event rates, revascularization frequency and bleeding rate.

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SUMMARY

CARDIOVASCULAR EVENT ASSESSMENT IN PATIENTS WITH NONOBSTRUCTIVE CORONARY ARTERY DISEASE UNDERGOING DUAL ANTIPLATELET TREATMENT

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Keywords: nonobstructive coronary artery disease, acute coronary syndrome, dual antiplatelet therapy, cardiovascular events.

РЕЗЮМЕ

КАРДИО-ВАСКУЛЯРНЫЕ СОБЫТИЯ У ПАЦИЕНТОВ С НЕОБСТРУКТИВНЫМ КОРОНАРНЫМ ЗАБОЛЕВАНИЕМ НА ФОНЕ ДВОЙНОГО АНТИТРОМБОЦИТАРНОГО ЛЕЧЕНИЯ

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Цель исследования - определение различия в клинических данных больных необструктивным и обструктивным острым коронарным синдромом для сравнения частоты развития различных кардио-васкулярных событий и основных конечных точек.

Исследовано 165 пациентов: 115 - с необструктивным, 50 – с обструктивным заболеванием коронарных артерий. Критерии включения в исследование: возраст >18лет; наличие любого атеросклеротического стеноза, больше, чем 20%, но меньше чем 50% в левой главной коронарной артерии, и больше, чем 20%, но меньше чем 70% в любой другой главной эпикардиальной коронарной артерии. Пациенты распределены на три группы: группа А - 55 пациентов с необструктивным острым коронарным синдромом, которые получали двойное антитромбоцитарное лечение – аспирин 100-160 мг в день и клопидогрел 75 мг в день, группа В - 60 пациентов с необструктивным острым коронарным синдромом, которые получали аспирин 100-160 мг в день, группа С - 50 пациентов с обструктивным острым коронарным синдромом, которым проводилось стандартное лечение. Исследованы клинические и демографические данные (возраст и пол). Сопутствующие заболевания включали диабет, гиперлипидемию, гипертонию, ожирение и болезни сердца (стенокардия, сердечная недостаточность, инфаркт миокарда, проведенное коронарное шунтирование и чрескожное коронарное вмешательство), почечное заболевание и заболевание печени. Зарегистрированы изменения кардиограммы и начальные лабораторные данные. Пациенты категорированы по количеству поражённых коронарных артерий. Последующие обследования выполнены спустя один, два и три месяца и 1 год. Оценены основные конечные точки - серьезные неблагоприятные кардиальные события: госпитализация спустя год по причине инфаркта миокарда или других сердечно-сосудистых заболеваний, частота сердечно-сосудистой смерти, стентирование кровеносных сосудов, выживаемость. Изучены типы и частота кровотечения в период лечения и наблюдения. Оценка данных проведенного исследования позволяет сделать вывод, что комбинация клопидогрела и аспирина оказалась значительно более эффективной, чем аспирин в снижении частоты развития инфаркта миокарда, однако отмечалась значительная разница между группами относительно частоты кардио-васкулярных событий, кровеносной реваскуляризации и кровотечений.

რეზიუმე

კარდიოვასკულური მოვლენების შეფასება არაობსტრუქციული კორონარული დაავადებით პაციენტებში, რომლებსაც უტარდებოდა დუალური ანტიაგრეგაციული მკურნალობა

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კვლევის მიზანს წარმოადგენდა კლინიკური მონაცემების და პირველადი საბოლოო წერტილების შესწავლა პაციენტებში არაობსტრუქციული კორონარული დაავადებით.

კვლევაში მონაწილეობდა 165 პაციენტი: 115 – არაობსტრუქციული და 50 – ობსტრუქციული კორონარული დაავადებით. პაციენტები დაიყო სამ ჯგუფად: A ჯგუფში შევიდა 55 პაციენტი არაობსტრუქციული კორონარული დაავადებით, რომელთაც უტარდებოდა დუალური ანტიაგრეგაციული მკურნალობა: ასპირინი 100-160 მგ 1-ჯერ დღეში და 75 მგ კლოპიდოგრელი 1-ჯერ დღეში. B ჯგუფში შევიდა 60 პაციენტი არაობსტრუქციული კორონარული დაავადებით, რომლებიც ღებულობდნენ მხოლოდ 100-160 მგ ასპირინს 1-ჯერ დღეში, C ჯგუფში მოხვდა 50 პაციენტი ობსტრუქციული კორონარული დაავადებით, რომელთაც უტარდებოდა გაიდლაინებით მოწოდებული მკურნალობა. ყველა პაციენტს ჩაუტარდა კორონარული ანგიოგრაფია. პაციენტები განაწილებული იყო დაზიანებული კორონარების რაოდენობის მიხედვით. შესწავლილია დემოგრაფიული მონაცემები, თანმხლები დაავადებები და ლაბორატორიული მონაცემები: ჰემატოლოგია, ლიპიდები, უზმოდ გლუკოზა და HbA1C, eGFR და კრეატინინი, ღვიძლის ფუნქციები. შესწავლილია ძირითადი კარდიოვასკულური მოვლენების განვითარების სიხშირე: მიოკარდიუმის ინფარქტი, რევასკულარიზაცია, კარდიოვასკულური სიკვდილობა, ასევე სისხლდენის განვითარების ხასიათი და სიხშირე. კვლევის შედეგებმა აჩვენა, რომ დუალურმა ანტიაგრეგაციულმა მკურნალობამ არ გამოავლინა სარწმუნო განსხვავება ასპირინთან შედარებით მიოკარდიუმის ინფარქტის განვითრების თვალსაზრისით, მაგრამ სარწმუნოდ შეამცირა კარდიოვასკულური მოვლენების და სისხლდენის სიხშირე.

THE LEFT VENTRICULAR SYSTOLIC FUNCTION AMONG PATIENTS WITH STEMI AFTER DIFFERENT TYPES OF TREATMENT STRATEGIES

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Cardiovascular diseases (CVD) are remaining at the leading positions in the structure of morbidity and mortality in the world. Despite significant advances in modern cardiology in improving the treatment of patients with ischemic heart disease (IHD), its clinical form – acute myocardial infarction (AMI) is a potentially fatal event and cause of death among adults [1].

This pathology is classified by the World Health Organization as one of the most important non-communicable diseases. By definition, the acute myocardial infarction with stable ST segment elevation (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) differ only in patterns of acute ischemia and myocardial necrosis on ECG. In the future, it determines the treatment tactics, but does not affect the AMI diagnostic protocol [2].

The main method of STEMI treatment is the restoration of blood flow patency in the occluded infarct-dependent artery. This can be achieved by pharmacological method. There is used thrombolytic therapy or mechanically which involve primary percutaneous coronary intervention (PPCI), or a combination of these methods of pharmaco-invasive reperfusion strategy. The use of a particular method of reperfusion is determined by the time elapsed from the beginning of manifestations of AMI and the clinical situation. Primary percutaneous coronary intervention, in accordance with the recommendations, is the preferred treatment strategy for the firs 120 minutes after the onset of clinical AMI manifestations [3].

Reperfusion is not always possible in real clinical practice. This is primarily due to the inevitable technical difficulties and secondly, the late seek of patients for medical care. According to the registers, the percentage of reperfusion therapy ranges from 77% to 95% [4,5].

Left ventricular function is an important predictor of the AMI outcome. In the studies the determination of left ventricular ejection fraction was shown to be a powerful predictor of total mortality during the observation period. Even with the successful reperfusion, the problem of the development of adverse postinfarction left ventricular remodeling does not lose its relevance. Risk assessment of systolic dysfunction among patients with STEMI after different types of treatment strategies is an important task of practical cardiology, which determined the purpose of this study [6,7].

The aim of the study - determine parameters the left ventricular systolic function among patients with STEMI after different types of treatment strategies.

Material and methods. The results of the study are based on the data obtained from a comprehensive examination of 447

patients with IHD: with stable ST-Segment elevation (STEMI - 280 patients), 91 ones with NSTEMI and the control group consisted of 76 persons with angina pectoris (II FC and III FC, 38 people per each). Screening of patients was carried out at the base of Municipal institution "Regional medical center of cardiovascular diseases" Zaporizhzhia Regional Council in the period from 2015 to January 2018 year. All 447 examined persons were comparable by age, social status and sex (the ratio of men to women was 4 to 1).

The criteria for inclusion in the study are male and female patients' age is from 46 to 75 years; postmenopausal women age is more than 1 year; the presence of AMI in the first 12 hours from the onset; informed consent of the patient to engage in the study.

Criteria for exclusion from the study: atrioventricular block of II-III degree; permanent form of atrial fibrillation; detection of congenital and acquired hemodynamically significan heart defects; stage III of chronic heart failure; discovered aneurysm of the left ventricle; decompensated comorbidity; acute inflammatory diseases or exacerbation of chronic; history of coronary artery bypass grafting; oncological disease.

All patients underwent complex clinical, instrumental and laboratory examinations. Verificati n of the AMI diagnosis was performed based on the ESC/ACCF/AHA/WHF Third universal definition of myocardial infarction (2012), taking into account the recommendations of the ESC Fourth universal definition of myocardial infarction (2018) [8,9]. The patients were divided into groups after the establishment of the compliance of patients regarding the criteria for inclusion/exclusion from the study depending on the presence/or absence of ST-Segment elevation and stable CHD:

The patients were divided into groups after the establishment of the compliance of patients regarding the criteria for inclusion/exclusion from the study depending on the presence of ST-Segment elevation and stable IHD: the first group included 280 patients with STEMI (median age was 60.0 [53.0 ; 64.0] years); the second group consists of 91 patients with NSTEMI (median age was 61.0 [56.0 ; 66.0] years); the third group include**s** of 76 patients with stable IHD (average age is 62,0 [57,0-65,0] year).

The risk of death of patients was calculated on the GRAEME 2.0 scale (Global Registry of Acute Coronary Events). The median values of scores on this scale had a noticeable difference between the groups of examined patients, and amounted to 104.5 [91.0-115.0] points in the group of STEMI patients versus 85.0 [75.0-95.0] points in the group of NSTEMI patients ($p<0.05$).

The level of MB-CPK in STEMI patients was 47.63 [24.10 ; 96.75] U/l and was considerably higher than the level of 32.70 [19.72 ; 45.45] U/l in the NSTEMI group ($p<0.05$). The median level of troponin I was 4.90 [0.92 ; 6.81] ng/ml in the group of STEMI patients and was significantly higher compared to the value of 1.28 [0.63 ; 3.29] ng/ml in the group of NSTEMI patients ($p<0.05$).

Echocardiographic study was carried out on the Vivid 3 Expert device (General Electric, USA) in M - and B-modes using a sensor 3S with a frequency of 1.5-3.6 MHz by conventional techniques EACVI (European Association of Cardiovascular Imaging), ASE (the American Society of Echocardiography). Determined parameters the left ventricular (LV) systolic function: end-systolic and end-diastolic LV volumes (LVVd, LVVs), stroke volume (SV), calculated the left ventricle ejection fraction (LVEF) using Simpson's method [10].

Patients were treated in conformity with the recommendations of ESC (2012, 2017), according to the order No. 455 of the Ukraine's Ministry of health dated 02.07.2014 and No. 164 of the Ministry of health of Ukraine dated 03.03.2016. In the group of patients with STEMI was the following therapy: combination of thrombolytic therapy and stenting were among 66 (23.6%) patients, systemic thrombolytic therapy was performed among 75 (26.8%) patients, stenting was among 109 (38.9%) patients and conservative treatment was among 30 (10.7%) patients. The follow-up treatment was carried out with the anticoagulants, antiaggregants, selective β-blocker, inhibitors of angiotensin converting enzyme, lipid-lowering drugs and nitrates.

The obtained data had a different distribution from the normal, and are presented in the form of median (Me) and inter quartile Me range [Q25 ; Q75]. The results of the study were processed by parametric or nonparametric statistics depending on the sample allocation using specialized computer applications ApacheOpenOffic (version 4.1) and PSPP (version 0.10.2, GNU Project, 1998-2016).

While comparing more than two independent variables, they used a variance analysis (One-way ANOVA), followed by a posteriori test. Equality of variances was checked using Leven's test. They used the criterion Scheff while equality of variances in the studied groups, and they used to test T2-Tamhane while the absence of equality of variances was. In the case of distribution of data distinct from normal, they used the analogue of dispersion analysis by the Krukal-Wallis method followed by post-hoc analysis using the Dunn criterion.

The relative risk (RR, Relative Risk and its 95% CI) was calculated using table 2x2 as the ratio of the frequency of cases among the patients exposed to the studied factor to the frequency of cases among the subjects not affected by this factor. The values of 95% CI RR were considered reliable, did not cross 1. In RR < 1, the risk of adverse course of the disease is lower than in persons not exposed to the factor, and in > 1 the probability of adverse course of the disease in the risk factor group is higher.

Results and discussion. We analyzed the left ventricular systolic function among the examined patients. The results are given in Table 1.

LVVd was no significant difference lower in the STEMI group: 108,65 [88,51 ; 126,45] cm^3, both against the value of 110,50 [88,17 ; 135,70] cm^3 in the NSTEMI group and against the value of 114,10 [103,40 ; 130,60] among stable IHD patients ($p>0.05$). The value of LVVs was significan - ly higher in the NSTEMI group: 47,90 [36,00 ; 62,10] cm^3, against the value of 38,54 [31,47 : 50,46] cm^3 in the group of stable IHD ($p<0.05$), but was no significant difference vs. the median of 47,72 [38,63 ; 57,47] cm^3 in the STEMI group ($p>0.05$).

SV was no significant difference in the STEMI group: 57,65 [46,27 ; 69,71] cm^3 against the value of 58,20 [48,62 ; 72,40] cm^3 in the NSTEMI group ($p>0.05$). When compared with the median of 73,93 [64,85 ; 86,00] in the group of stable IHD , the value in the STEMI group was significant 22.0% lower, and in the NSTEMI group it was significant 21.1% lower ($p<0.05$). Ejection fraction of the left ventricle in the group of STEMI patients was significantly lower and amounted to 53,32 [48,66 ; 60,37] against 65,10 [59,98 ; 68,94] in the group of patients with stable IHD, but was no significan difference vs. the median of 55,68 [47,73 ; 61,02]% in the NSTEMI group ($p>0.05$).

Then we evaluated dynamics of the left ventricular systolic function among patients with STEMI depending on the obtained therapy. The results are presented in Table 2.

Table 1. The parameters of left ventricular systolic function among the examined patients (Me [Q_{25}-Q_{75}], n=447)

Variable	STEMI (n=280)	NSTEMI (n=91)	Stable IHD (n=76)
	1	2	3
LVVd, cm³	108,65 [88,51 ; 126,45]	110,50 [88,17 ; 135,70]	114,10 [103,40 ; 130,60]
P-value	p = 0,10		
LVVs, cm³	47,72 [38,63 ; 57,47]	47,90 [36,00 ; 62,10]	38,54 [31,47 : 50,46]
P-value	p_{1-2} = 1,0	p_{2-3} < 0,001	p_{1-3} < 0,001
SV, cm³	57,65 [46,27 ; 69,71]	58,20 [48,62 ; 72,40]	73,93 [64,85 ; 86,00]
P-value	p_{1-2} = 1,0	p_{2-3} < 0,001	p_{1-3} < 0,001
LVEF,%	53,32 [48,66 ; 60,37]	55,68 [47,73 ; 61,02]	65,10 [59,98 ; 68,94]
P-value	p_{1-2} = 1,0	p_{2-3} < 0,001	p_{1-3} < 0,001

Table 2. Dynamics of the left ventricular systolic function among patients with STEMI (Me [Q_{25};Q_{75}], n=280)

Variable		Combination therapy (n=66)	Thrombolytic therapy (n=75)	Stenting (n=109)	Conservative treatment (n=30)	P-value
		1	2	3	4	
LVVd, cm³	1 day	105,25 [77,66 ; 120,90]	114,50 [99,69 ; 129,80]	107,50 [86,53 ; 120,10]	108,65 [90,59 ; 126,60]	p=0,08
	14 day	95,35 [76,32 ; 115,80]*	112,30 [92,90 ; 130,00]*	103,60 [83,17 ; 120,70]*	103,20 [87,55 ; 122,00]	p_{1-2}=0,01; p_{2-3}=0,29 p_{1-3}=0,87; p_{3-4}=1,0 p_{1-4}=0,67; p_{2-4}=1,0
	Δ%	-4,78 [-9,52 ; 0,27]	-2,32 [-5,21 ; 1,72]	-3,83 [-6,95 ; 1,18]	-2,86 [-4,19 ; 5,88]	
LVVs, cm³	1 day	45,41 [36,60 ; 56,30]	51,01 [36,83 ;63,35]	46,96 [40,08 ; 56,16]	50,94 [42,55 ; 68,40]	p = 0,13
	14 day	42,93 [35,96 ; 55,56]*	50,61 [38,17 ; 67,43]*	45,89 [37,85 ; 57,36]	53,65 [45,60 ; 79,45]*	p_{1-2}=0,09; p_{2-3}=0,14 p_{1-3}=1,0; p_{3-4}=0,02 p_{1-4}=0,01; p_{2-4}=1,0
	Δ%	-3,03 [-8,04 ; 3,44]	-2,28 [-4,21 ; 8,61]	-3,14 [-8,12 ; 2,38]	11,03 [4,12 ; 17,97]	
SV, cm³	1 day	53,96 [42,89 ; 67,39]	62,69 [50,36 ;70,50]	56,99 [46,26 ; 71,18]	57,34 [47,53 ; 68,44]	p=0,08
	14 day	46,56 [39,56 ; 62,75]*	56,90 [42,26 ; 71,79]*	53,14 [42,19 ; 70,35]*	45,45 [36,81 ; 61,00]*	p=0,09
	Δ%	-4,41 [-14,17 ; 0,60]	-5,35 [-15,67 ; 0,11]	-4,48 [-10,07 ; 0,68]	-14,21 [-19,46 ; -8,12]	
LVEF,%	1 day	53,47 [48,77 ; 58,20]	52,86 [47,17 ; 62,00]	54,35 [50,30 ; 61,30]	50,80 [46,71 ; 55,64]	p=0,09
	14 day	52,18 [47,81 ; 57,70]*	52,28 [45,85 ; 59,92]*	55,05 [48,48 ; 61,50]	46,07 [38,45 ; 50,61]*	p_{1-2}=0,99; p_{2-3}=0,24 p_{1-3}=0,37; p_{3-4}<0,001 p_{1-4}<0,001; p_{2-4}0,001
	Δ%	-2,44 [-6,99 ; 2,23]	-3,30 [-8,02 ; 0,34]	0,44 [-3,78 ; 2,25]	-13,58 [-21,62 ; -8,59]	

*note: * - the validity of the change is Variable in dynamics (p<0,05)*

Table 3. The relative risk of systolic dysfunction among patients with STEMI

Subgroups	RR	95% CI RR
Combination therapy	0.260	0.122-0.552
Thrombolytic therapy	0.486	0.276-0.856
Stenting	0.216	0.110-0.426

There was in screening no significant difference between subgroups on such variables as LVVd, LVVs, SV and LVEF (p>0.05). There was no significant difference between subgroups on such indicator as SV after 14 day (p>0.05). The lowest ejection fraction was among patients who received conservative treatment 46,07 [38,45-50,61]%, at the same time a significant difference was achieved with three types of reperfusion: against combination therapy, where LVEF was 52,18 [47,81-57,70]% (p<0.05); against thrombolytic therapy - 52,28 [45,85-59,92]%, (p<0.05); against stenting - 55,05 [48,48-61,50]%, (p<0.05). We did not find any differences between the LVEF subgroups reperfusion (p>0.05).

Methods of reperfusion therapy were evaluated as a factor which is capable of reducing the risk of left ventricular systolic dysfunction. The LVEF value, which was regarded as systolic dysfunction, was taken as < 45% by Simpson's method. The results are presented in table 3.

Subgroup conservative treatment included 14 patients with LV EF below 45% and 16 patients with LV EF above 45%, in subgroup combination therapy respectively were 8 patients with LV EF below 45% and 58 above 45%, relative risk systolic dysfunction was 0.260, 95% CI 0.122-0.552. In subgroup thrombolytic therapy, there were 17 patients with LV EF below 45% and 58 patients had LV EF over 45%, relative risk systolic dysfunction was 0.486, 95% CI 0.276-0.856. Subgroup stenting included 11 patients with LV EF below 45% and 98 patients had LV EF over 45%, relative risk systolic dysfunction was 0.216, 95% CI 0.110-0.426.

Evaluation of early cardiac remodeling among patients with STEMI is an important precursor to the unfavorable course of AMI, namely recurrence coronary events or death. Therefore, the scientific search in this direction continues [1, 12].

The results obtained are correlated with the thesis that today PPSI is the most effective method to achieve a full reperfusion of infarct-dependent artery. At present, meta-analyses of studies have convincingly proved the significantly greater effectiveness of PPSI in reducing mortality and improving hospital and long-term prognosis in comparison with thrombolytic therapy. Therefore, the strategy of early revascularization in STEMI is one of the most important approaches to the treatment of this category of patients [13].

Currently, there is an active search for predictors of LV EF recovery after AMI. So in the study of D.S. Chew et al. was show that among patients with first presentation AMI, the absence of LV EF recovery is independently associated with increased risk of serious events in follow-up, including a nearly 6-fold risk of nonfatal and fatal cardiac arrest, or over a 4-fold risk of all-cause mortality [14].

Thus, the obvious advantages of one reperfusion strategy over another can be obtained only in sufficientl large samples of patients or in certain cohorts of patients. Despite the fact that the contribution of AMI to the development of the remodeling process of the myocardium is set, however, is not well defined peculiarities of structural-geometric reshaping of the left ventricle in these patients, and not indicated the dependence on the depth and extensiveness of the myocardial damage that requires further scientific research and continue studies

Conclusions.

1. STEMI patients have lower left ventricular ejection fraction than patients with stable IHD, which is associated with the process of early myocardial remodeling after AMI.

2. The reduction of the relative risk of systolic dysfunction occurs in reperfusion therapy, most strongly when using stenting - RR 0.216, 95% CI 0.110-0.426.

Prospects for further research. Recently, the possibility of predicting serious events and ways to prevent adverse it has been actively studied. Further study of the dynamics of the left ventricular systolic function through the state of recovery will allow us to develop optimal management tactics for patients after AMI, this will improve the prognosis and reduce the development of recurrent cardiovascular events, which requires continued research.

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SUMMARY

THE LEFT VENTRICULAR SYSTOLIC FUNCTION AMONG PATIENTS WITH STEMI AFTER DIFFERENT TYPES OF TREATMENT STRATEGIES

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The aim of the study - to determine parameters the left ventricular systolic function among patients with STEMI after different types of treatment strategies.

The results of the study are based on the data obtained from a comprehensive examination of 447 patients with IHD: STEMI - 280 patients, 91 ones with NSTEMI and the control group consisted of 76 persons with angina pectoris. The study evaluated the risk of death of patients (GRAEME 2.0 scale), levels of MB-CPK and troponin I, LVEF and other echocardiographic parameters for various reperfusion tactics.

The results obtained are correlated with the thesis that today PPSI is the most effective method to achieve a full reperfusion of infarct-dependent artery. The study showed greater effectiv - ness of PPSI in reducing mortality and improving hospital and long-term prognosis in comparison with thrombolytic therapy.

The reduction of the relative risk of systolic dysfunction occurs in reperfusion therapy, most strongly when using stenting - RR 0.216, 95% CI 0.110-0.426.

Keywords: Ischemic heart disease, STEMI, relative risk, reperfusion therapy, systolic dysfunction.

РЕЗЮМЕ

СИСТОЛИЧЕСКАЯ ФУНКЦИЯ ЛЕВОГО ЖЕЛУДОЧКА У БОЛЬНЫХ СО STEMI ПОСЛЕ РАЗЛИЧНЫХ СТРАТЕГИЙ ЛЕЧЕНИЯ

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Цель исследования - определить параметры систолической функции левого желудочка у пациентов со STEMI после различных стратегий лечения.

Результаты исследования основаны на данных, полученных в результате комплексного обследования 447 пациентов с ишемической болезнью сердца: STEMI - 280 пациентов, 91 пациент с NSTEMI и контрольная группа - 76 больных стенокардией. В исследовании оценивались риск смерти пациентов (шкала GRAEME 2.0), уровни MB-CPK и тропонина I, фракция выброса левого желудочка и другие эхокардиографические параметры для различных тактик лечения и реперфузии.

Полученные результаты коррелируют с тезисом о том, что на сегодняшний день PPSI является наиболее эффективным методом для достижения полной реперфузии инфаркт-зависимой артерии. Исследование показало большую эффективность PPSI в снижении смертности и улучшении долгосрочного прогноза в сравнении с тромболитической терапией.

Результаты проведенного исследования позволяют заключить, что снижение относительного риска систолической дисфункции миокарда левого желудочка при применении реперфузионной терапии наиболее выраженно проявилось при стентировании (RR 0.216, 95% CI 0.110-0.426).

რეზიუმე

მარცხენა პარკუჭის სისტოლური ფუნქცია პაციენტებში STEMI-ით მკურნალობის სხვადასხვა სტრატეგიის შემდეგ

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კვლევის მიზანს წარმოადგენდა მარცხენა პარკუჭის სისტოლური ფუნქციის პარამეტრების შეფასება პაციენტებში STEMI-ით მკურნალობის სხვადასხვა სტრატეგიის შემდეგ.

კვლევის შედეგები ეფუძნება გულის იშემიური დაავადების მქონე 447 პაციენტის კომპლექსური გამოკვლევის მონაცემებს: STEMI - 280 პაციენტი, NSTEMI - 91 პაციენტი, საკონტროლო ჯგუფი – 76 პაციენტი სტენოკარდიით.

კვლევაში ფასდებოდა პაციენტების სიკვდილის რისკი (შკალა GRAEME 2.0), MB-CPK-ის და ტროპონინ I-ის დონე, მარცხენა პარკუჭის განდევნის ფრაქცია და სხვა ექოკარდიოგრაფიული პარამეტრები მკურნალობისა და რეპერფუზიის სხვადასხვა ტაქტიკის დროს.

მიღებული შედეგები კორელირებს თეზისთან იმის შესახებ, რომ სადღეისოდ PPSI წარმოადგენს ყველაზე ეფექტურ მეთოდს ინფარქტ-დამოკიდებული არტერიის სრული რეპერფუზიის მიღწევისათვის. კვლევამ აჩვენა PPSI-ის დიდი ეფექტურობა სიკვდილობის შემცირებისა და გრძელვადიანი პროგნოზის გაუმჯობესებისათვის, თრომბოლიზურ თერაპიასთან შედარებით.

ჩატარებული კვლევის შედეგების საფუძველზე ავტორები დაასკვნიან, რომ მიოკარდიუმის მარცხენა პარკუჭის სისტოლური დისფუნქციის შეფარდებითი რისკის შემცირება რეპერფუზიული თერაპიის გამოყენებისას ყველაზე მკაფიოდ გამოვლინდა სტენტირების დროს (RR 0.216, 95% CI 0.110-0.426).

EFFICACY OF SPIRONOLACTONE IN ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH RESISTANT HYPERTENSION IN COMBINATION WITH RHEUMATOID ARTHRITIS

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The influence of concomitant pathology on the development and progression of hypertension (H) in recent years has attracted researchers` attention. H is found twice as often and is characterized by poorer control and frequent combination with resistant hypertension (RH) in patients with rheumatoid arthritis (RA) [35]. 51% of patients with RA have a significant increase in cardiovascular risk even in the absence of concomitant cardiovascular pathology. The risk of ischemic cardiac events is comparable to that of diabetes mellitus [3].

Increased inflam atory activity is associated with the development of diastolic heart failure (HF) in patients with H [13, 27]. T cells play an important role in the pathogenesis of H and HF, with various stimuli leading to the formation of effector T cells, which together with monocytes and macrophages penetrate into arterial walls. Increased levels of a number of cytokines (interleukin-6, interleukin-17, interleukin-10, tumor necrosis factor-α, and interferon-γ) contribute to the damage and aging of blood vessels and cardiomyocytes, which causes their fibrosis and hypertrophy. Cross-reactions between natural killer cells, adaptive immune cells, and innate immune cells contribute to myocardial damage and dysfunction [25]. On the other hand, the activation of the renin-angiotensin-aldosterone system and the increase in the level of transforming growth factor-β stimulate the deposition of the extracellular matrix in patients with H, which causes perivascular fibrosis of the heart [5]

The treatment of patients with H remains a difficul issue in cardiology. According to the latest data, only half of the patients with H in the general population reach the target levels of blood pressure (BP) [10]. However, the achievement of the target level of BP occurs only in 42% in patients with RA [35]. There are no data on the frequency and features of RH in patients with RA in different populations

A decrease in sodium levels and an increase in potassium levels have a positive effect on the level and profile of BP in patients with H [6, 32]. As many as a third of patients with H were diagnosed with primary hyperaldosteronism, which makes the use of aldosterone blockers pathogenetically justified. A diffe - entiated treatment approach occurs in the presence of RH [23]. Experimental studies have shown that chronic administration of aldosterone to rats induced myocardial fibrosis in the hypertrophied left ventricle (LV), even under conditions of normotension. Administration of spironolactone (aldosterone antagonist) has an antifibroti effect [7, 8, 33]. Spironolactone together with the other antihypertensive drugs can prevent or reduce myocardial fibrosis [38], improve cardiovascular prognosis [17], which requires comprehensive studies in a cohort of patients with coexistence of RH with RA.

The aim of the study was to investigate the antihypertensive efficac , structural and functional remodeling of the heart in patients with RH in combination with RA after 12-month combination therapy, including angiotensin-converting enzyme (ACE) inhibitor, calcium channel blocker, diuretics, aldosterone receptor blocker (spironolactone) and immunosuppressive drug (methotrexate).

Materials and methods. The analysis of medical documentation (outpatient medical cards and medical histories) was performed, patients who met the inclusion criteria and were able to provide informed consent were selected. Possible causes of secondary H were excluded. Initially, the study involved 101 patients with RA and H, whom at a pre-screening visit were adjusted the dose of the basic disease-modifying drug (all RA patients received methotrexate 15 mg per week), when necessary. Doses of antihypertensive drugs (ACE inhibitors, calcium channel blocker and/or diuretic) were added or increased as required. 60 patients were selected after 1 month. They were on the triple antihypertensive drug therapy (with mandatory inclusion of diuretics) in maximal and submaximal doses, did not reach the target BP levels, and met the criteria for RH. According to the prescribed treatment, patients were divided into two groups: the main group and the comparison group, randomly. 12.5 mg of spironolactone was added to the existing triple therapy once daily with an increase in dose after 1 month to 25 mg (group 1, n=30). Treatment or left unchanged (without spironolactone) in group 2 (n=30). The duration of therapy was 12 months. The strategy for the diagnosis and treatment of RA was determined according to EULAR 2019 criteria [29]. The diagnosis of H was established on the basis of the 2018 ESC/ESH recommendations. Target levels of offic BP was established (for systolic BP (SBP) <140 mm Hg and or diastolic BP (DBP) <90 mm Hg). The goal of SBP should be <130 mm Hg and/or DBP <80 mm Hg according to the results of 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) [34, 37]. RH was diagnosed as uncontrolled despite optimal doses of 3 classes of antihypertensive drugs, including thiazide diuretics, or if 4 or more antihypertensive drugs of different classes are required for adequate BP control [2].

A randomized, parallel-group prospective study was conducted to investigate the clinical effectiveness of spironolactone in 60 patients (mean age 61.9±9.1 years; 84.6% women) patients with RA and RH.

Inclusion criteria: age 45-74 years, patients with stage II RH and RA, receiving disease-modifying therapy - methotrexate, chronic kidney disease (CKD) not higher than stage II (GFR not less than 60 ml/min/1.73 m^2), K + serum level from 3.0 to 5.0 mmol/l, informed consent to participate in the study.

Exclusion criteria: stage 3 H, history of CKD III-V, acute renal damage, endocrine pathology (diabetes mellitus, Addison's disease, etc.), clinical signs of hypovolemia, offic SBP <115 mm Hg or DBP <55 mm Hg, atrial fibrillation, and flutte , AV blocks 2nd and 3rd degree when performing an ECG, classes III and IV of chronic HF according to NYHA, decreased LV ejection fraction (<40%) or valvular heart disease, acute myocardial infarction or other cardiovascular events (Q wave myocardial infarction, non-Q wave myocardial infarction, unstable angina), myocardial revascularization, stroke, transient ischemic attack) in the anamnesis, alcoholism, drug or mental disorders, infectious diseases, active chronic diarrhea, oncological and hematological diseases, active phases of diseases of the gastrointestinal tract, gout, liver, K^+ serum> 5.0 mmol/l, Na^+ serum <130 mmol/l, inability to give informed consent to participate in the study.

All patients were evaluated by general clinical, laboratory, and instrumental methods of examination. Complete blood count, urinalysis, blood glucose, lipid profile, K+, Na+, Cl-, creatinine, urea, AST, bilirubin, total protein, C-reactive protein (CRP), and

electrocardiography (ECG) were performed. All patients signed an informed consent to participate in the study. The Helsinki Declaration (2000) and international standards for research were taken into account.

All patients underwent offic blood pressure (BP) measurement. 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) was performed using ABPM50 (Heaco, Great Britain) with an oscillometric measurement method to assess BP levels. SBP, DBP, and pulse blood pressure (PBP) were determined. Doppler echocardiography was performed with an Arietta S60 devise (Aloka-Hitachi) and a 2.5 - 3.5 MHz transducer. The main indicators of the structure and geometry of the heart were determined: left atrial volume (LAV), left atrial volume index (LAVI) by the formula: LAVI= LAV /BSA (where BSA is the body surface area and was calculated by the modified Dubois-Dubois formula (BSA = 0,007184 * Weight (kg) 0,425 * Height (cm) 0,725), the thickness of an interventricular septum (IVS), a posterior wall of LV (PW), LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV stroke volume (LVSV). LV mass (LVM) was calculated by the modified formula of R. Devereux: LVM = 0.8 * (1.04 * (LVEDD + IVS + PW)^3-LVEDD^3))) + 0.6, LVM index (LVMI) according to the formula: LVMI = LVM/ BSA, relative wall thickness (RWT) according to the formula: RWT= 2 * PW / LVEDD, LV fractional shortening (FS), LV midwall fractional shortening (mFS), LV chamber dilatation (LVEDV/BSA).

We categorized patients into 4 groups based on LAVI: without LA dilatation (16-28 ml/m^2), slight increase (29-33 ml/m^2), moderate increase (34-39 ml/m^2) and severe increase (≥40 ml/m^2). The types of LV geometry were assessed from RWT, LVMI and LVEDV/ BSA values [4]: concentric LV hypertrophy (LVH) with dilatation (RWT≥0.42, LVMI ≥115 g/m^2 in men and ≥95 g/m^2 in women, LVEDV /BSA ≥74 ml/m^2 in men, LVEDV /BSA ≥ 68 ml/m^2 in women); concentric LVH without dilatation (RWT ≥0.42, LVMI ≥115 g/m^2 in men and ≥95 g/m^2 in women, LVEDV /BSA <74 ml/m^2 in men, LVEDV /BSA <68 ml/m^2 in women); eccentric LVH with dilatation (RWT <0.42, LVMI ≥115 g/m^2 in men and ≥95 g/m^2 in women, LVEDV /BSA ≥74 ml/m^2 in men, LVEDV /BSA ≥68 ml/m^2 in women); eccentric LVH without dilatation (RWT<0.42, LVMI ≥115 g/m^2 in men and ≥95 g/m^2 in women, LVEDV /BSA <74 ml/m^2 in men, LVEDV /BSA <68 ml/m^2 in women); normal LV geometry (RWT <0.42, LVMI <115 g/m^2 in men and <95 g/m^2 in women, LVEDV /BSA <74 ml/m^2 in men, LVEDV /BSA <68 ml/m^2 in women).

Evaluation of left ventricular diastolic function (LVDF) and right ventricle (RV) was performed according to the assessment of transmitral blood flow from the apical 4-chamber position on the mitral and tricuspid valves, respectively, using pulsed-wave Doppler and Continuous-Wave Doppler. The peak modal velocity in early diastole (peak E, cm sec) and the peak modal velocity in late diastole (peak A, cm/sec), the ratio of early to late transmitral diastolic velocity (E/A), the deceleration time of E (DT, msec), and time of LV isovolumetric relaxation time (IVRT, msec) were determined. Peak systolic mitral annular velocity at the lateral and medial parts of the mitral annulus (s ‘lat and s’ med, respectively, cm/sec), as well as early diastolic myocardial velocity at the lateral and medial parts of the mitral annulus (e ‘lat and e’ med, respectively, cm/sec) and late diastolic myocardial velocity at the lateral and medial parts of mitral annulus (a ‘lat and a’ med, respectively, cm/sec) were determined using tissue Doppler to better assess diastolic function. The average values of these indicators were calculated as their half-sum (S ‘, E’, and A’ respectively). Tricuspid regurgitation (TR) was also taken into account [19, 24, 28, 31].

The primary endpoints were highlighted as improved BP control, better diastolic function (E/A, DT, E/e’), and myocardial remodeling (decline of LVMI, LVEDV/ BSA, LAVI) in Doppler echocardiography after 12 months. The groups of patients with RA and RH were comparable in age, sex, duration of RA and H, RA activity by CRP level and DAS28-CRP scale, which corresponded to high disease activity in both cases, Steinbrocker radiological stage, stage of functional impairment (FI), smoking status, the necessity to take nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCs), Table1.

Statistical processing of the results was performed with the

Table 1. Clinical characteristics of patients with RH in combination with RA

	Group 1 (n=30)	**Group 2** (n=30)
Mean Age, years, M ± σ	60,5 ± 8,5	63,4 ± 9,6
Gender (female), n (%)	26 (86,7)	24 (80,0)
Seropositive RA, n (%)	26 (86,7)	22 (73,3)
DAS28-CRP, M ± σ	5,3 ± 1,0	5,5 ± 0,9
X-ray stage II, n (%)	9 (30,0)	8 (26,7)
X-ray stage III, n (%)	15 (50,0)	17 (56,7)
X-ray stage IV, n (%)	6 (20,0)	5 (16,7)
FI stage I, n(%)	8 (26,7)	7 (23,3)
FI stage II, n (%)	17 (56,7)	19 (63,3)
FI stage III, n (%)	5 (16,7)	4 (13,3)
NSAIDs, n (%)	24 (80,0)	22 (73,3)
GCs, n (%)	10 (33,3)	12 (40,0)
RA duration, years, M ± σ	10,9 ± 6,6	8,4 ± 6,1
H duration, years, M ± σ	9,8 ± 6,7	11,3 ± 7,5
I stage of H, n (%)	27 (90,0)	28 (93,3)
II stage of H, n (%)	3 (10,0)	2 (6,7)
Smoking status, n (%)	5 (16,3)	6 (20,0)

Table 2. Systemic hemodynamic parameters in patients of the main and comparison groups before and after 12 months of therapy, M±σ

	Group 1 (n = 30)		Group 2 (n = 30)	
	before treatment	after treatment	before treatment	after treatment
Office S , mm Hg	143,0±6,4	125,9±6,1**	140,8±7,6	132,6±4,4**
Office D , mm Hg.	84,4±5,1	72,8±4,0***	84,0±6,5	80,0±6,3**
Office P , mm Hg	58,5±6,6	53,1±5,6**	56,8±8,0	52,6±7,5***
SBP by ABPM, mm Hg	140,8±8,7	123,9±3,9**	141,7±6,4	133,2±4,6*
DBP by ABPM, mm Hg	83,1±6,7	73,8±4,5**	81,9±9,7	76,4±7,6
PBP by ABPM, mm Hg	57,7±7,1	50,1±4,3*	59,8±11,0	56,8±7,8

*notes (here and in tables 4, 5): * - P <0,05, ** - P <0,01, *** - P <0,001 in comparison with values of data before treatment*

help of Statistics SPSS 22. The normality of the distribution was assessed using the Shapiro-Wilk test. Under the condition of the normal distribution of the studied trait in the sample, parametric statistical methods were used. The mean value of the indicator (M), standard deviation (σ), standard error (SE), and 95% confidence interval for the mean (95% CI) were determined for descriptive statistics. The t-test for related samples was used to compare the mean values. When distributing of the trait was different from normal, nonparametric statistics was used. We choose the values of the median (Me), 25 and 75 quartiles (Q25 - Q75) for the descriptive part. Variables were expressed as a percentage (%) for categorical part. The Mann-Whitney U-test was used to compare the two independent groups. A comparison of groups on qualitative binary data was performed using Pearson's chi-squared (χ^2) test (corrected by Yates) and Fisher's exact test.

Results and discussion. Prior to inclusion in the study, the groups were comparable in terms of BP. The target level of office BP was achieved in 26 (86.7%) patients versus 12 (40.0%) patients (χ^2 = 12.6, p <0.001) in the group of 12-month antihypertensive therapy with spironolactone compared with treatment without it. This could be due to the corresponding changes in the offic BP. Offic SBP, DBP and PBP were significantly reduced by 11.9%, 13.7%, and 8.7%, in patients of group 1 respectively (in group 2 - by 5.7%, 4.6%, and 4.0%). Therefore, there was a more pronounced decrease in SBP and DBP in 2.1 and 2.9 times in patients who additionally took spironolactone compared with the group of patients who did not take it (Table 2). Taking into account "harder" indicators of ABPM, the target BP was recorded in 26 (86.7%) and 9 (30.0%) patients after treatment, respectively groups 1 and 2. After spironolactone therapy, the mean SBP, DBP, and PBP were likely dwindled by 11.8%, 17.8%, and 5.4% against the less significant dynamics of group 2, while only SBP reduced statistically significantly - by 8.8%. The findings were confirmed in a study by Roongsritong C., 2005, where SBP remained unchanged in the placebo group, while in the spironolactone group it was reduced from 144 ± 22 to 138±15 mm Hg after 4 months of treatment [28].

Thus, in patients with RH in combination with RA, the addition of spironolactone to standard antihypertensive therapy for 12 months leaded to a significant reduction in BP and reaching its target level in 86.7% of cases, which improved cardiovascular prognosis.

It should be noted that in the group with spironolactone no electrolyte disturbances were obtained. In patients of group 1, the level of potassium did not exceed the reference ranges. It was slightly increased from 4.7 (4.2-5.0) to 4.8 (4.4-5.2) mmol/l (p=0.02), which corresponded to the results of another study, that showed an increase in potassium levels by 0.2 mmol/l (p <0.001) in patients with diastolic type of HF [9]. The level of sodium on spironolactone therapy remained unchanged: 145.0 (141.0-146.0) mmol/l against 145.0 (141.0-147.0) mmol/l (p = 0.8). In patients of group 2 there was a constant level of potassium: 4.5 (4.2-5.0) mmol/l against 4.5 (4.2-5.0) mmol/l (p = 0.3), but the sodium level increaseed from 143.0 (140.0-145.0) mmol/l to 146.0 (142.5-150.0) mmol/l (p = 0.01), indicating a potential prohypertensive effect caused by sodium retention

The next stage of the work was the assessment of changes in the structural and functional state of the heart on different treatment options in patients with RH in combination with RA. According to recent studies, the size of the left atrium (LA) is an independent factor in predicting cardiovascular disease and heart failure. That`s why, determining the dynamics of the frequency and stage of LA dilatation is strategic during the treatment [1, 21, 22]. LA dilatation at the beginning of research was defined at 26 (86.7%) patients in group 1, as well as in group 2. Patients with moderate LA dilatation (11 (36.7%) cases) and severe increase (10 (33.3%) patients) were the majority of all. A slight increase of LA was registered less often - in 5 (16.7%) people. There was a decrease in the number of patients with LA dilatation after 12 months of treatment in group 1: it was determined in 19 (63.3%) people (χ^2 = 4.4, p = 0.037). There was a drop in a number of patients with severe and moderate stages of LA dilatation (1.5 (22.2%) and 2.8 times (13.3%) respectively), and an increase in the mild stage of LA dilatation - 1.8 times (30.0%) of patients. A positive dynamics was not observed in group 2. LA dilatation was defined in 25 (83.3%) of patients. Given that LAVI indirectly reflects the state of LV diastolic function, a significant decrease in its value in group 1 by 18.3% against the absence of shifts in group 2, maight indicate a significant contribution of spironolactone in improving LV relaxation function in patients with RH and RA. It should be noted that the RV dimension of on long-term therapy in both groups of patients did not change.

At the time of inclusion in the study in groups 1 and 2, LVH was detected in 27 (90.0%) and 26 (86.7%) patients, respectively. Severe LVH was dominated in the structure of LVH in both groups (Table 3). The frequency of LVH detection declined by 10% (χ^2=3.9, p=0.048) in patients of group 1 due to a 1.8-fold reduction in the frequency of detection of severe LVH. The most common was eccentric LVH with LV dilatation in group 1 before the treatment, which indicated a worse prognosis for patients with the development of HF [20, 36]. The frequency of its reduced by 2.2 times after 12 months of therapy. Aa number of patients with concentric LVH with LV dilatation diminished by 2.5 times. Opposite changes were observed in group 2. Despite the lowering of BP, hypertensive LV remodeling continued its progression: the distribution of detection of concentric LV without dilatation of the LV increased (χ^2=3.3, p=0.04) (Table 3).

Changes in the parameters of the geometry and frequency of

Table 3. Distribution in patients of the main and comparison groups before and after 12 months of therapy according to the stage of LVH and the type of LV remodeling, n (%)

	Group 1 (n=30)		Group 2 (n=30)	
	before treatment	after treatment	before treatment	after treatment
Mild LVH, n (%)	2 (6,7%)	2 (6,7%)	4 (13,3%)	5 (16,7%)
Moderate LVH, n (%)	1 (3,3%)	9 (30,0%)***	6 (20,0%)	4 (13,3%)
Severe LVH, n (%)	24 (80,0%)	13 (43,3%)***	16 (53,3%)	20 (66,7%)
No LVH, n (%)	3 (10,0%)	6 (20,0%)*	4 (13,3%)	1 (3,3%)
Eccentric LVH with dilatation, n (%)	11 (36,7%)	5 (16,7%)***	9 (30,0%)	7 (23,3%)
Concentric LVH without dilatation, n (%)	8 (26,7%)	(23,3%)	8 (26,7%)	13 (43,3%)**
Concentric LVH with dilatation, n (%)	5 (16,7%)	2 (6,7%)**	5 (16,7%)	4 (13,3%)
Eccentric LVH without dilatation, n (%)	3 (10,0%)	10 (33,3%)***	4 (13,3%)	5 (16,7%)

*notes: * - P <0,05, ** - P <0,01, *** - P <0,001 in comparison with values of data before treatment*

Table 4. Parameters of the structural and functional state of the heart in patients of the main and comparable groups before and after 12 months of therapy, Me (25% - 75%)

	Group 1 (n=30)		**Group 2 (n=30)**	
	before treatment	**after treatment**	**before treatment**	**after treatment**
LAVI, ml/m^2	39,4 (31,9-45,1)	32,3 (24,2-39,4)**	40,6 (32,8-46,2)	40,2 (31,8-49,6)
IVS, mm	12,0 (11,0-13,0)	11,0 (9,0-11,0)**	11,1 (10,0-12,5)	11,0 (10,0-12,0)
PW, mm	10,4 (9,0-11,0)	9,7 (9,0-11,0)**	10,3 (9,0-11,0)	10,2 (10,0-11,0)
LVM, g	266,7 (206,0-307,0)	227,9 (175,0-278,0)**	238,0 (192,5-269,5)	235,1 (210,5-266,5)
LVMI, g/m^2	141,7 (122,2-157,6)	122,8 (98,0-149,0)**	127,9 (104,4-149,0)	128,3 (119,8-143,8)
LVEDV/BSA, ml/m^2	69,9 (58,8-78,4)	64,1 (53,2-71,2)**	67,6 (57,7-76,6)	68,2 (56,5-76,0)
FS, %	31,6 (28,4-35,6)	36,5 (33,0-39,3)**	36,5 (29,9-41,9)	33,7 (30,1-36,6)
mFS, %	17,1 (14,0-20,1)	20,7 (18,0-24,3)**	16,7 (12,7-21,5)	18,2 (14,6-21,4)
LV EF, %	59,3 (58,4-63,1)	64,0 (60,4-67,9)**	60,3 (54,9-65,0)	61,0 (55,8-64,9)

LVH were reflected in the dynamics of the values of LV structural and functional parameters. Analysis of the dynamics of data representing the stage of LVH showed concordance with the antihypertensive efficac of the combined treatment of patients in both groups. There was a decrease in LVM and LVMI by 13.9% (-38.7 g) and 13.0% (-18.9 g / m^2, both p <0.01) in patients of group 1 in the absence of probable changes in patients of group 2. A lowering in the thickness of its walls (respectively IVS and PW by 2.3 mm (17.3%) and 1.75 mm (15.2%), both p <0.01)) was detected in group 1 at torpidity these indicators in group 2 (Table 4).

The values of the LV contractile were within the reference range in patients of both groups. However, the data that reflects the regional contractility (FS and mFS) were likely to increase by 15.5% and 21%, respectively, and the global LV contractility (EF) - by 7.9% (all p <0, 01) after 12 months of therapy in patients of group 1 in the absence of the dynamics of these figures in group 2

ALDO-DHF, a randomized, prospective study, involving 422 elderly outpatients, the vast majority of whom had H, showed that the addition of spironolactone to antihypertensive therapy for 12 month leaded to a regression of LVH (decrease in LVMI by 6 g / m^2, p = 0.009), but did not improve the quality of life and did not reduce the frequency of hospitalizations [9]. The informativeness of\ the LV relaxation index (E / e') had been proven even in masked uncontrolled H. The value of E / e' diminished from 12.7 to 12.1 (p <0.01), which indicated an improvement in LVDF [14]. The lower antihypertrophic efficac of treatment in this study may be due to a lower dose of spironolactone (25 mg/day without titration), a lower baseline LVH, and the fact that not all patients had RH.

Similar results were obtained in another study, which included 34 patients with RH and studied the effect of spironolactone at a dose of 25 mg with a titration of up to 50 mg per day for 6 months [12]. It was found that the pronounced antihypertrophic efficac of spironolactone did not depend on the level of aldosterone. However, there was no improvement in LVDF and the dynamics of connective tissue markers, which could be explained by a shorter duration of treatment and fewer patients involved.

In another study, patients with RH received spironolactone for 6 months [11]. Regardless of the concentration of aldosterone, a decrease in BP and a decline in the stage of LVH have been demonstrated. However, in patients with hyperaldosteronism, in addition to a pronounced diuretic effect, the reversal of LVH was identified mainly by reducing the stage of LV dilatation, while in patients with normal aldosterone concentration - by reducing wall thickness as well as stronger vasorelaxation.

Given that patients with H suffered the most from LV diastolic dysfunction (LVDD), it was interesting to analyze the effect of combination antihypertensive therapy on the LV relaxation in patients with RH and RA. The frequency of LVDD reduced from 25 (83.3%) to 12 (40.0%) (χ^2 = 11.9, p <0.001) in patients of the spironolactone group, which was accompanied by changes in its structure: decline in a number of patients with impaired LV relaxation, pseudonormal and restrictive types, respectively, from 18 (60.0%) to 11 (36.7%), from 6 (20.0%) to 1 (3.3%) and from 1 (3.3%) to its absence. LVDD was detected in 28 (93.3%) patients of group 2 before the treatment, impaired LV relaxation, pseudonormal and restrictive types - in 19 (63.3%), 8 (26.7%)

and 1 (3, 3%) patients, then after 12 months- in 26 (85.8%), 13 (42.9%), 11 (36.7%) 2 (6.6%) patients respectively, which indicated the lack of improvement of LVDF without the addition of an aldosterone antagonist.

These data were confirmed by analyzing the parameters of Doppler echocardiography that characterize LVDF. There was an increase in peak E and the ratio of E / A by 14.7% and 24.9%, respectively (both p <0,01), a drop in peak A, the value of DT, and TR by 6.9%, 15.1%, and 16.7%, respectively (all p <0.01) after 12 months of treatment in patients receiving spironolactone, which indicated an improvement of LVDF. No significant changes in the data characterizing LVDF in patients of group 2 were found. There were no statistical differences in the dynamics of diastolic function of the RV in both groups.

Tissue Doppler echocardiography (a more sensitive method of assessing LVDF) was used. Significant positive changes in LV relaxation function on spironolactone therapy in the 1 group were confirmed and characterized by an increasing in e' med, e' lat and E' by 26.7%, 23.1 % and 23.8%, respectively (all p <0.01), and decreasing E / e' med, E / e' lat and E / E' by 8.6%, 6.0% and 7.3%, respectively (all p <0,01). No significant improvement in LV DF was found in group 2. The characteristics of systolic and early diastolic myocardial velocities in the area of the mitral annulus did not differ in both groups and were compared with pre- and post-treatment (Table 5).

Spironolactone at a dose of 25 mg/day, even with a short course of administration (for 4 months), improved LVDF in elderly people with isolated LVDD. The value of E / A was increased (from 0.71 +/- 0.08 to 0.84 +/- 0.19, p = 0.025) and DT was decreased (from 285.5 +/- 73.1 to 230.0 +/- 54.7, p = 0.035) in the group of spironolactone treatment, which corresponded to the data obtained in another study [26]. Other researchers analyzed the results of 80 patients with a metabolic syndrome who took spironolactone 25 mg per day for 6 months. A decrease in E / e' (β = -0.21, p <0.03) and an increase in the peak E (β = -0.44, p <0.001) were noted, but E / A and DT remained unchanged [15, 16]. A German study evaluated the efficac of spironolactone in 213 patients with H at a dose of 25 mg/day with treatment for 12 months. It has been determined that such a period of therapy was sufficien to improve LVDF, which coincided with our results [9].

The results of 7 studies involving 4147 participants were analyzed in PubMed, EMBASE, and COCHRANE databases. Treatment of patients with H using spironolactone compared with placebo led to a lessening in E / e' (SD -1.38; 95% CI, -2.03 to -0.73; p <0.001) and an increase in E / A' (SD -0, 05; 95% CI, -0.10 to - 0.00; p = 0.03), which coincided with the data of our study. The fact that DT remained unchanged was interesting (SD 1.04; 95% CI, -8.27 to 10.35; p = 1.83). Improvement of LV relaxation may be associated with the additional antifibrotic effect of the aldosterone antagonist, which is especially inherent for patients with a combination of H and RA. The question of the duration of therapy with this diuretic to correct LVDD remains important. It was shown that for patients with H an improvement of LVDF (according to shifts in the E / A ratio) was observed on spironolactone therapy for > 6 months (SD -0.06; 95% CI, −0.11 to -0.00, p = 0.03) against its absence during therapy ≤ 6 months (SD -0.04; 95% CI, -0.18-0.10; p = 0.61) [18]. This was consistent with our results.

Along with the study of antihypertensive and antihypertrophic effe ts, the analysis of the effect of spironolactone on the clinical and laboratory activity of RA in patients with RH was performed. There was a decrease in RA activity: a decline in CRP from 6.4 (4.0-20.1) mg / l to 4.2 (2.0-11.6) mg / l (p = 0.04) and reduction in the DAS28-CRP from 5.6 (4.9-6.4) to 4.0 (3.4-5.0) (p <0.0001) in patients of group 1. In contrast, patients in group 2 did not have the dynamics of RA activity: CRP changed from 8.2 (3.2-16.6) mg / l to 10.9 (2.5-27.6) mg / l (p = 0.3) and the DAS28-CRP was 5.7 (5.0-6.1) against 5.6 (5.0-6.5) (p = 0.6). This may indicate an increase in the anti-inflammatory effect of long-term use of aldosterone antagonists. Our data were comparable with data from another study involving 24 RA patients (mean age 49 ± 1.8 years; disease duration 8.5 ± 5.8 years) with high RA activity on 12-week spironolactone 2 mg/kg /day therapy. The reduction of both the level of CRP from 15.2 ± 3.8 to 9.4 ± 2.6 mg / dl (p = 0.019) and the DAS28-CRP from 6.9 ± 0.25 to 4.1 ± 0.31 (p <0.05) was proved [30].

The number of patients with pericardial separation decreased

Table 5. Parameters of LV diastolic function in patients of the main and comparable groups before and after 12 months of therapy, Me (25% - 75%)

	Group 1 (n=30)		Group 2 (n=30)	
	before treatment	**after treatment**	**before treatment**	**after treatment**
LV E, cm / sec	66,9 (53,0-75,7)	75,4 (62,9-83,6)**	70,1 (54,2-85,1)	68,6 (54,2-77,4)
LV A, cm / sec	80,2 (64,6-95,4)	73,5 (61,0-83,0)**	75,2 (64,0-84,9)	75,0 (63,2-90,2)
LV E/A	0,9 (0,7-1,1)	1,1 (0,8-1,2)**	1,0 (0,7-1,2)	0,9 (0,7-1,1)
LV DT, msec	192,2 (160,0-220,0)	161,0 (136,0-180,0)**	184,4 (151,0-211,0)	183,6 (145,0-234,0)
LV IVRT, msec	92,8 (84,0-104,0)	90,7 (84,0-88,0)	89,8 (75,5-100,0)	88,0 (84,0-94,0)
e' med, cm / sec	9,1 (7,0-11,0)	11,3 (9,7-12,9)**	9,1 (7,1-10,7)	8,3 (6,6-10,0)
e' lat, cm / sec	10,0 (8,4-11,1)	12,1 (9,9-13,9)**	9,5 (7,6-10,7)	9,6 (8,3-10,8)
E', cm / sec	9,5 (8,5-10,5)	11,7 (10,3-12,9)**	9,3 (8,1-10,8)	9,0 (7,8-9,7)
E/ e' med	7,8 (5,8-8,6)	7,1 (5,3-7,5)**	8,8 (6,5-8,4)	8,3 (6,8-9,7)
E/e' lat	7,1 (5,3-8,4)	6,6 (5,2-7,7)**	7,6 (6,2-8,6)	7,7 (5,3-9,2)
E/E'	7,3 (5,9-8,1)	6,7 (5,6-7,3)**	7,7 (6,3-8,5)	7,8 (5,9-8,7)
TR, cm / sec	2,7 (2,4-3,0)	2,3 (2,2-2,7)**	2,5 (2,1-3,0)	2,5 (2,2-3,1)
S', cm / sec	7,4 (6,4-7,7)	7,0 (6,6-7,4)	7,6 (6,3-8,4)	7,1 (6,4-7,8)
A', cm / sec	9,0 (7,1-10,5)	8,9 (7,6-9,9)	9,6 (7,5-11,7)	8,9 (7,5-10,1)

from 11 (36.7%) to 3 (10.0%) ($\chi^2 = 8.0$, $p < 0.05$) in patients of group 1 after treatment. Dynamics of pericarditis was absent in patients of group 2 ($\chi^2 = 2.2$, $p = 0.137$). The more pronounced anti-inflammatory and diuretic effects of combined antihypertensive and immunosuppressive treatment with the addition of spironolactone were confirmed clinically and instrumentally in patients with RH in combination with RA.

Conclusions. Additional administration of an aldosterone blocker to standard triple antihypertensive therapy in patients with RH and RA is characterized by high antihypertensive efficacy - the target blood pressure is reached three times more often than in the comparison group, and safety - it is not accompanied by hyperkalemia and/or hypotension. Therapy with the inclusion of spironolactone shows a probable decrease in the mean SBP and DBP by 11.8% and 17.8%, respectively. The addition of spironolactone to therapy leads to a decline in the number of patients with LA dilatation by 23.4% ($\chi^2 = 4.4$, $p = 0.037$) and LVH by 10% ($\chi^2 = 3.9$, $p = 0.048$), which is combined with a decline in eccentric and concentric LV dilatation 2.2 and 2.5 times, respectively, with the progression of LV hypertensive remodeling in patients without spironolactone treatment: detection of concentric LVH without LV dilatation is increased by 16.7% ($\chi^2 = 3.3$, $p = 0.04$). Spironolactone leads to a lessening of LVH (by 13.0%, $p < 0.01$) by reducing the stage of LV dilatation (by 7.3%, $p < 0.01$) and wall thickness (IVS by 17.3% and PW by 15.2%, both $p < 0,01$). LVH regression is associated with an improvement in LV contractility, both regional (FS) and global (EF) - by 15.5% and 7.9%, respectively (both $p < 0.01$). There is a diminution in the incidence of LLDD by 43.0% ($\chi^2 = 11.9$, $p < 0.001$) and changes in its structure on spironolactone treatment: a lowering in the ratio of patients with impaired LV relaxation and pseudonormal LVDD by 23.3% and 16.7%, respectively (both $p < 0.05$). This is accompanied by a decline in E / e' med, E / e' lat and E / E' by 8.6%, 6.0% and 7.3%, respectively ($p < 0,01$), which indicates an improvement in LVDF. Potent antihypertensive and antihypertrophic effects of spironolactone are combined with increased anti-inflammatory action in patients with RH and RA. It is expressed by a decrease in clinical and laboratory activity of RA: the DAS28-CRP lessens from 5.6 (4.9-6.4) to 4.0 (3.4-5.0) ($p < 0.001$).

We consider that it is appropriate to conduct further studies with a larger sample of patients and a wider range of laboratory markers to clarify the relationship between aldosterone receptor blockade and mechanisms of the antihypertensive effect in patients with RA and RH, given the positive effect of spironolactone on hypertrophy, dilatation, and diastolic dysfunction.

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SUMMARY

EFFICACY OF SPIRONOLACTONE IN ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH RESISTANT HYPERTENSION IN COMBINATION WITH RHEUMATOID ARTHRITIS

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The aim of the study is to investigate the antihypertensive efficac , structural and functional remodeling of the heart in patients with resistant hypertension (RH) and rheumatoid arthritis (RA) after 12-month of therapy.

The treatment includes angiotensin-converting enzyme inhibitor, calcium channel blocker, diuretics, aldosterone receptor blocker (spironolactone), and immunosuppressive drug (methotrexate). 101 patients with hypertension (H) and RA were examined at the screening visit. 60 patients (mean age 61.9±9.1 years; 84.6% of women) meeting the criteria for RH were selected after 1 month. A randomized, controlled, parallel-group prospective study was conducted. Patients underwent general clinical, laboratory, and Doppler echocardiography investigations. They were divided into 2 groups: the main group, which represented patients whom to the basic antihypertensive therapy were added spironolactone 25 mg/day (group 1, n=30), and the comparison group, which represented patients who continued antihypertensive treatment without the addition of spironolactone (group 2, n=30) with 12- monthly observation. Groups of patients are comparable in age, sex, duration of RA and H, RA activity. The target blood pressure was achieved in 86.7% against 30.0% of patients ($p < 0.001$) on spironolactone treatment compared to the inclusion of it. Therapy with spironolactone shown a probable decrease in the mean systolic blood pressure, diastolic blood pressure, and pulse blood pressure by 11.8%, 17.8%, and 5.4%, respectively. There was a reduction in the number of patients with left atrium dilatation from 86.7% to 63.3% ($\chi^2=4.4$, $p=0.037$) in group 1. The frequency of left ventricular hypertrophy (LVH) dropped by 10% ($\chi^2=3.9$, $p=0.048$) in patients of group 1. The incidence of eccentric LVH with left ventricular (LV) dilatation decreased by 2.2 times, concentric LVH with LV dilatation declined by 2.5 times after treatment in group 1. There was a further LV hypertensive remodeling in group 2: detection of concentric LVH without LV dilatation ($\chi^2=3.3$, $p=0.04$) was increased. There was a reduction of LV mass index (by 13.0%, $p<0.01$) due to a decrease in the stage of LV dilatation (by 7.3%, $p<0.01$), and the thickness of its walls (respectively interventricular septum and posterior wall by 17.3% and 15.2%, both $p<0.01$) in spironolactone group with the absence of probable changes in group 2. The LV contractile capacity, both regional fractional shortening and global ejection fraction improved (decline by 15.5% and 7.9% (both $p<0.01$)) in group 1 in the absence of dynamics in group 2. The incidence of LV diastolic dysfunction subsided from 83.3% to 40.0% ($\chi^2=11.9$, $p<0.001$) in patients of the spironolactone group, mainly due to a probable lessening in a number of patients with an abnormal LV relaxation from 60.0% to 36.7%. There was a lowering in E/e' med, E/e' lat and E/E' by 8.6%, 6.0% and 7.3%, respectively (all p

<0.01) in patients on spironolactone therapy, which reflected the improvement of LV diastolic function. Patients of group 1 demonstrated a de-escalation of RA activity: a dropping of the DAS28-CRP from 5.6 (4.9-6.4) to 4.0 (3.4-5.0) (p<0,0001) in the absence of its dynamics in patients of group 2 (from 5.7 (5.0-6.1) to 5.6 (5.0-6.5) (p=0.6)).

The addition of spironolactone to basic therapy demonstrates increased antihypertensive efficac and potent antihypertrophic efficac . These effects are combined with improved systolic and diastolic LV function and a decrease of clinical and laboratory activity of RA in elderly patients with RH in combination with RA.

Keywords: resistant arterial hypertension, rheumatoid arthritis, spironolactone, left ventricular diastolic dysfunction.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ СПИРОНОЛАКТОНА В СОСТАВЕ КОМБИНИРОВАННННОЙ АНТИГИПЕРТЕНЗИВНОЙ ТЕРАПИИ У БОЛЬНЫХ РЕЗИСТЕНТНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В СОЧЕТАНИИ С РЕВМАТОИДНЫМ АРТРИТОМ

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Целью исследования является изучение антигипертензивной эффективности и структурно-функциональной перестройки сердца у больных резистентной артериальной гипертензией и ревматоидным артритом (РА) на фоне 12-месячной комбинированной терапии, включающей: ингибитор ангиотензин превращающего фактора, блокатор кальциевых каналов, диуретик, антагонист альдостерона (спиронолактон) и иммуносупрессор (метотрексат). На скрининговом визите обследован 101 пациент с артериальной гипертензией (АГ) и ревматоидным артритом (РА). Спустя 1 мес. отобраны 60 пациентов, средний возраст 61,9±9,1 г., 51 (84,6%) женщина и 9 (15,4%) мужчин, соответствующие критериям резистентной артериальной гипертензии (РАГ). Проспективное, рандомизированное исследование проведено в параллельных группах. Пациентам проведены обще-клиническое, лабораторное и допплерэхокардиографическое исследования. Больные разделены на 2 группы: I группа (основная) (n=30) – пациенты, к базисной антигипертензивной терапии которых добавлялся спиронолактон 25 мг/сут, II группа (сравнения, n=30), - пациенты, продолжившие антигипертензивное лечение без добавления спиронолактона с 12-месячным наблюдением. Группы больных сопоставимы по возрасту, полу, варианту РА, продолжительности РА и АГ, активности РА. На фоне терапии с включением спиронолактона в сравнении с лечением без него целевой уровень АД достигнут у 26 (86,7%) больных против 9 (30,0%) больных, (p<0,001). Терапия с включением спиронолактона демонстрирует достоверное снижение среднесуточных систолического, диастолического и пульсового артериального давления на 11,8%, 17,8% и 5,4%, соответственно. В I группе наблюдалось уменьшение числа больных с дилатацией левого предсердия с 86,7% до 63,3% (χ^2=4,4, p=0,037). У больных I группы частота гипертрофии левого желудочка (ГЛЖ) уменьшилась на 10% (χ^2=3,9, p=0,048). После лечения в I группе уменьшились частота выявления эксцентричной ГЛЖ с дилатацией левого желудочка (ЛЖ) в 2,2 раза и концентрической ГЛЖ с дилатацией ЛЖ в 2,5 раза. У пациентов II группы отмечается дальнейшее гипертензивное ремоделирование ЛЖ: увеличивается выявление концентрической ГЛЖ без дилатации ЛЖ (χ^2=3,3, p=0,04). У пациентов группы спиронолактона отмечается уменьшение индекса массы миокарда ЛЖ на 13,0%, (p<0,01) за счет уменьшения степени дилатации ЛЖ (на 7,3%, p<0,01), и толщины его стенок (согласно межжелудочковой перегородке и задней стенке ЛЖ на 17,3% и 15,2%, в обеих случаях p<0,01) при отсутствии достоверных сдвигов у больных II группы. У больных I группы улучшилась сократительная способность ЛЖ: регионарное фракционное укорочение и глобальная фракция выброса - на 15,5% и 7,9%, соответственно, (p<0,01) при отсутствии динамики во II группе. На фоне лечения у больных группы спиронолактона частота выявления диастолической дисфункции ЛЖ уменьшается с 83,3% до 40,0% (χ^2=11,9, p<0,001) преимущественно за счет возможного уменьшения доли аномального расслабления ЛЖ с 60,0% до 36,7%. На фоне терапии спиронолактоном отмечается уменьшение E/e' med, E/e' lat и E/E', соответственно, на 8,6%, на 6,0% и 7,3% (p<0,01), что отражает улучшение диастолической функции ЛЖ. На фоне лечения у больных I группы наблюдается уменьшение активности РА: снижение значения индекса DAS28-СРБ с 5,6 (4,9-6,4) баллов до 4,0 (3,4-5,0) баллов (p<0,0001) при отсутствии его динамики у больных II группы - с 5,7 (5,0-6,1) до 5,6 (5,0-6,5) баллов (p=0,6).

У больных старшего возраста с РАГ в сочетании с РА добавление к базисной терапии спиронолактона демонстрирует усиление антигипертензивной эффективности, мощную антигипертрофическую эффективность, что сочетается с улучшением систоло-диастолической функции ЛЖ и снижением клинико-лабораторной активности РА.

რეზიუმე

სპირონოლაქტონის ეფექტურობა კომბინირებულ ანტიჰიპერტეზიულ თერაპიაში პაციენტებში რევმატოიდულ ართრიტთან შერწყმული რეზისტენტული არტერიული ჰიპერტენზიით

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კვლევის მიზანს წარმოადგენდა ანტიჰიპერტენზიული ეფექტურობის და გულის სტრუქტურულ-ფუნქციური გარდაქმნების შეფასება პაციენტებში რეზისტენტული არტერიული ჰიპერტენზიით და რევმატოიდული ართრიტით 12-თვიანი კომბინირებული თერაპიის ფონზე, რაც მოიცავდა: ანგიოტენზინ-გარდამქმნელი ფაქტორის ინჰიბიტორს, კალციუმის არხების ბლოკატორს, დიურეტიკს, ალდოსტერონის ანტაგონისტს (სპირონოლაქტონი) და იმუნოსუპრესორს (მეტოტრექსატი). სკრინინგულ ვიზიტზე გამოკვლეული იყო 101 პაციენტი არტერიული ჰიპერტენზიით და რევმატოიდული ართრიტით. 1 თვის შემდეგ შერჩეული იყო 60 პაციენტი (საშუალო ასაკი - 61,9±9,1 წელი, 51 (84,6%) ქალი და 9 (15,4%) მამაკაცი), რომლებიც შეესაბამებოდა რეზისტენტული არტერიული ჰიპერ-

ტენზიის კრიტერიუმებს. პროსპექტული, რანდომიზებული კვლევა ჩატარდა ორ პარალელურ ჯგუფში. პაციენტებს ჩაუტარდა საერთო კლინიკური, ლაბორატორიული და დოპლერექოკარდიოგრაფიული კვლევა. პაციენტები დაიყო ორ ჯგუფად: I ჯგუფი (ძირითადი, n=30) – პაციენტები, რომელთა ბაზისურ თერაპიას დამატებული ჰქონდა სპირონოლაქტონი – 25 მგ/დღეში, II ჯგუფი (შედარების, n=30) – პაციენტები, რომლებიც აგრძელებდნენ ანტიჰიპერტენზიულ მკურნალობას სპირონოლაქტონის დამატების გარეშე 12-თვიანი დაკვირვების პერიოდში.

თერაპიაში სპირონოლაქტონის ჩართვის ფონზე არტერიული წნევის სამიზნე დონე მიღწეული იქნა 26 პაციენტში (86,7%) (*vs* 9 (30%); p<0,001). სპირონოლაქტონის ჩართვა განსაზღვრავს სისტოლური, დიასტოლური და პულსური არტერიული წნევის საშუალო დღეღამური მაჩვენებლების სარწმუნო შემცირებას 11,8%-ით, 17,8%-ით და 5,4%-ით, შესაბამისად. I ჯგუფში აღინიშნა პაციენტების რაოდენობის შემცირება მარცხენა წინაგულის დილატაციით 86,7%-დან 63,3%-მდე (χ^2=4,4, p=0,037). ამავე ჯგუფში მარცხენა პარკუჭის ჰიპერტროფიის სიხშირე შემცირდა 10%-ით (χ^2=3,9, p=0,048). მკურნალობის შემდეგ I ჯგუფში შემცირდა მარცხენა პარკუჭის ექსცენტრული ჰიპერტროფიის, მარცხენა პარკუჭის დილატაციით, გამოვლენის სიხშირე 2,2-ჯერ, მარცხენა პარკუჭის კონცენტრული ჰიპერტროფიის, მარცხენა პარკუჭის დილატაციით, გამოვლენის სიხშირე კი - 2,5-ჯერ. II ჯგუფის პაციენტებში აღინიშნება შემდგომი ჰიპერტენზიული რემოდელირება: იმატებს მარცხენა პარკუჭის კონცენტრული ჰიპერტროფიის გამოვლინება მარცხენა პარკუჭის დილატაციის გარეშე (χ^2=3,3, p=0,04). სპირონოლაქტონის ჯგუფის პაციენტებში აღინიშნება მარცხენა პარკუჭის მიოკარდიუმის მასის ინდექსის შემცირება 13,0%-ით (p<0,01) მარცხენა პარკუჭის დილატაციის ხარისხის შემცირების (7,3%-ით, p<0,01) და მისი კედლების სისქის (პარკუჭთშორისი ძგიდის და მარცხენა პარკუჭის უკანა კედლის მიხედვით, 17,3%-ით და 15,2%-ით, ორივე შემთხვევაში p<0,01) ხარჯზე. I ჯგუფის პაციენტებს გაუმჯობესდათ მარცხენა პარკუჭის კუმშვადი აქტივობა: რეგიონული ფრაქციული დამოკლება და განდევნის გლობალური ფრაქცია – 15,5%-ით და 7,9%-ით (p<0,01), შესაბამისად, II ჯგუფში დინამიკის არარსებობის ფონზე. სპირონოლაქტონით მკურნალობის ფონზე აღინიშნება E/e' med-ის, E/e' lat-ის და E/E'-ის შემცირება, შესაბამისად, 8,6%-ით, 6,0%-ით და 7,3%-ით (p<0,01), რაც ასახავს მარცხენა პარკუჭის დიასტოლური ფუნქციის გაუმჯობესებას. I ჯგუფის პაციენტებში მკურნალობის ფონზე აღინიშნება რევმატოიდული ართრიტის აქტივობის შემცირება (5,6 ქულიდან 4,0 ქულამდე) ამ მაჩვენებლის დინამიკის არარსებობისას II ჯგუფის პაციენტებში (5,7 ქულიდან 5,6 ქულამდე) (p=0,6).

უფროსი ასაკის პაციენტებში რეზისტენტული არტერიული ჰიპერტენზიით და რევმატოიდული ართრიტით ბაზისურ თერაპიაში სპირონოლაქტონის ჩართვა ზრდის ანტიჰიპერტენზიულ ეფექტურობას, ავლენს მძლავრ ანტიჰიპერტროფიულ ეფექტურობას, რაც შერწყმულია მარცხენა პარკუჭის სისტოლურ-დიასტოლური ფუნქციის გაუმჯობესებასთან და რევმატოიდული ართრიტის კლინიკურ-ლაბორატორიული აქტივობის შემცირებასთან.

COMORBID CONDITION – DIABETES MELLITUS WITH CO-EXISTENT RAYNAUD'S SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Comorbidity (from Latin "co" – along with, "morbus" – disease) is defined as the co-existence of two and/or more syndromes (trans-syndromal comorbidity) or diseases (trans-nosological comorbidity), which are pathogenically interrelated or simultaneous (chronological comorbidity), in a single patient. The most common comorbidities in patients with rheumatic diseases include cardiovascular diseases (CVD), liver and biliary tract infection, lung diseases, amyloidosis, fractures of diffe - ent localizations, malignant neoplasms, metabolic disorders and diabetes mellitus (DM) [11].

According to the Ministry of Health of Ukraine, rheumatoid arthritis (RA) affected an estimated 112,960 individuals (49,420 people of working age) in 2016 [16]. In other words, the prevalence of RA in Ukraine is 340 cases per 100,000 adult population. Women are 3-4 times more likely to develop RA than men; however, in seropositive patients (rheumatoid factor (RF)+) and elderly people, these gender differences are less obvious [15].

On one hand, the inflammatory process is accompanied by the formation of a great number of cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), that induce the synthesis of C-reactive protein (CRP) which increases the expression of cell adhesion molecules in endothelial cells and promotes attachment of leukocytes to the endothelium [20]. On the other hand, there is a correlation between the presence and activity level of non-specific inflam ation and the development of metabolic syndrome (MS) (obesity, arterial hypertension, dyslipidemia and DM) [15].

According to Ivanytskyi I.V., patients with RA present with higher plasma levels of cholesterol and blood glucose as compared to those with deforming osteoarthritis, reactive arthritis [13,15].

Since the main mechanisms involved in the pathogenesis of RA with co-existent DM are complex defects in T-cell immunoregulation and B-cell tolerance manifesting themselves as an imbalance in the production of proinflammatory and anti-inflamatory cytokines resulting in chronic systemic inflammation [8], and the number of such patients constantly increases, scientists pay more attention to determining the common pathogenic mechanisms of these diseases. The acceleration of atherogenesis due to local inflammation of the vessel wall on the background of persistent autoimmune inflamma ion and impaired lipid transport and metabolism was proven to occur more frequently in patients with RA on the background of DM [7].

In 58.7-72% of patients with RA, comorbid conditions such as Raynaud's syndrome (RS) which can significantly modify the clinical course of the disease, worsen treatment efficac and reduce both quality of life and life expectancy, are diagnosed [21].

Microcirculatory changes play an important role in the pathogenesis of RA, while the microcirculatory system acts as a target organ where the immune, inflammatory and metabolic mechanisms of the pathological process are realized. Disturbances of the microcirculation are associated with systemic disorders, disease duration, impaired antioxidant defense, endothelial dysfunction (ED) parameters and reliably play the leading role in the pathogenesis of RA systemic manifestations. The endothelium, which reduces endothelium-dependent vasodilation, thereby facilitating the increase in the rate of cellular processes and accelerating their apoptosis, is a major target of oxidative stress.

Numerous recent studies have demonstrated that both ED and increased intima-media thickness are predictors of potential cardiovascular morbidity among the general population serving as one of the diagnostic criteria for early detection of atherosclerotic vascular lesions [12]. In RA, ED is observed even at its early stages, and, therefore, it is interpreted as a sign of accelerated development of atherosclerosis as well. Thus, the presence of ED is considered as one of the first manifestations of atherogenesis in patients with RA [5, 6, 18].

Since in the development of RS multifactorial mechanisms are involved, its etiology is certainly unknown. Vascular and immune mechanisms play an important role. Local tissue ischemia with a potential development of dystrophy, that is observed in RS, can occur due to dysregulation of vascular functions by the sympathetic nervous system or due to increased formation of vasoconstrictor substances in the process of autoimmune inflamation. In the inflammatory process, vascular changes consist in endothelial proliferation or destruction, intimal hyperplasia or thickening resulting in tissue ischemization [2, 4].

Therefore, further study of the clinical course of DM and RS in patients with RA is relevant as it allows us to optimize the correction schemes in combination therapy for such patients.

The aim of study was to investigate the clinical course of DM and RS in patients with RA using laboratory and instrumental research methods.

Material and methods. There were examined 85 (12 males and 73 females) patients with RA who were treated in the rheumatology department of Ivano-Frankivsk Central City Clinical Hospital. The patients' age ranged from 40 to 70 years; the average age was 45.7±2.3 RS was diagnosed in 47 (9 males and 38 females) patients. The average duration of RA was 9.3±2.4 years. RA was diagnosed based on the 2010 American College of Rheumatology classification criteria. To diagnose RS, Allen and Brown's criteria were used [10]; to diagnose DM, the official diagnostic criteria for DM were used [3, 14].

All the patients were divided into 2 groups: Group I comprised 38 patients with RA; Group II included 47 patients with RA and co-existent RS. Group II was further divided into two subgroups: Group IIa included 32 patients with RA and secondary RS; Group IIb comprised 15 patients with RA, co-existent RS and DM. In addition, there were examined 25 apparently healthy individuals of the same age who presented with normal values of the parameters studied.

The content of endothelin-1 (ET-1) was determined using enzyme immunoassay (EIA) by means of a reagent kit manufactured by Peninsula Laboratories Inc. (USA). It is a sandwich EIA strategy to detect the free forms of human ET-1. The concentration of TNF-α was determined using a standard EIA by means of CytELISA TNF-α reagent kit (USA).

The levels of CRP and RF were determined using the latex agglutination test. To determine the concentration of CRP in mg/l in the sample, the highest dilution of the serum with visible agglutination should be multiplied by 6 mg/l. The value below 6 mg/l is considered normal; the sensitivity of the test is 6 mg/l. To determine the amount of RF in mIU/ml in the sample, the highest dilution of the serum with visible agglutination should be multiplied by 12 mIU/ml. The value below 12 mIU/ml is considered normal; the sensitivity of the test is 12 mIU/ml.

Endothelial function was evaluated using so-called endothelium-dependent vasodilation of the brachial artery (EDVBA). The reactivity test was performed according to the method of Celermajer et al. (1992). Brachial artery flow-mediated dilation by 10% and more on the background of reactive hyperemia was considered as normal response of the brachial artery, while lower values were considered as pathology [9].

To objectify the assessment of RS in patients with RA, nailfold capillaroscopy was applied. The open capillary index (OCI), that reflects the ratio of functioning capillary loops to capillary loops with a reduction in the number of capillaries was calculated. The OCI of 50-70% is considered normal.

To assess the state of the peripheral circulation, the rating scale proposed by Shcherbakov A.B. (1987) was used. The scale of RS attack severity is a 10-point visual analogue scale with 0 points representing the total absence of attacks and 10 points indicating gangrenous changes in the fingers. The frequency and duration of RS attacks were assessed as well.

Blood glucose level was determined by a private laboratory Prima Med by means of BioChem FC-360 (normal blood glucose ranges from 3.3 to 5.5 mmol/l); the level of glycosylated hemoglobin (HbA1c) was determined using the A15 (BioSystems) analyzer (normal HbA1c ranges from 3.8 to 6.5 mmol/l).

The study was conducted in accordance with the basic bioethical provisions of the Helsinki Declaration of the World Medical Association on the ethical principles of scientific 549 medical research involving human (2013) and the order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, which was confirmed by the findings of the meeting of the Ethical Commission of Ivano-Frankivsk national medical university, Ivano-Frankivsk.

Research materials were statistically processed using the methods of biostatistics in STATISTICA (StatSoft Inc, USA) with the determination of the arithmetic mean, its mean squared deviation and standard error of the mean. The statistically significant difference (p) between the studied groups was determined using the Student's t-test. To identify the relationships between variable data, the correlation coefficient (r) was determine

Results and discussion. ED signs were observed in 76 (89.4%) patients (Table 1). ED was diagnosed in all patients with

RA, co-existent RS and DM. In the patients with RA and those with RA and co-existent RS, impaired EDVBA was detected. In the patients of Group II, the indicator of EDVBA (6.5±0.2%) was significantly lower as compared to the patients of Group I (8.8±0.3%) (p<0.05). This was most likely due to constant vasospastic attacks causing endothelial integrity impairment.

In the patients with RA and secondary RS, the level of ET-1 was 1.7 times higher than that in the patients without RS (p<0.05) and 2 times higher as compared to the patients of Group IIb. This indicated a higher risk of endothelial damage in the patients of Group II. The concentration of ET-1 in the patients with RA, co-existent RS and DM correlated with RA activity (r=0.65, p<0.05).

TNF-α is a well-known pro-inflammatory cytokine. Therefore, the degree of the inflammatory process activity is of the greatest importance for assessing the level of TNF-α. In the patients with minimal activity of the pathological process, this indicator increased by 2.1 times as compared to healthy donors; in moderate activity of inflammat ry syndrome, TNF-α level increased even more; in maximum activity of the pathological process and in case of DM co-existence, the level of TNF-α increased to 83.6±1.4 pg/ml. The level of this cytokine was found to be significantl higher (by 20.0%) in the patients of Group II as compared to Group I. There was a strong correlation between the degree of RA activity and the level of TNF-α (r=0.73; p<0.01) in the patients with RA and secondary RS. Summarizing the information mentioned above, we can assert that TNF-α is an important pro-inflammatory agent the increased production of which in RA aggravates the clinical course of the disease. There was observed a correlation between the level of TNF-α and the degree of inflammatory syndrome activity in the patients with RA, DM and secondary RS. Persistently high serum concentration of TNF-α in patients with secondary RS is an unfavorable prognostic sign and predictor of RA progression.

The levels of both CRP and TNF-α, serving as non-specific inflammatory markers, were significantly higher (29.37±3.56 mg/l, p<0.01) in the patients with RS as compared to the patients with RA only (23.89±1.77 mg/l). This indicated high RA activity in the patients of Group II.

An important factor predicting the course of RA with co-existent secondary RS and DM is the presence of high HbA1c titers. When comparing the indicators in Group I and Group II, the increase in blood glucose levels was observed. In the patients of Group IIa without DM, HbA1c level was (5.8±0.2); in the patients of Group IIb, it constituted (7.1±2.12) being significantly higher (p<0.05) than that in the patients of Group I (5.05±1.14) (Table 1).

In RA patients with secondary RS without DM, blood glucose level, on the background of empirical treatment, was within a critical range (5.9±0.5; p<0.05) mmol/l and differed significan - ly from that in the patients of Group I and Group IIb, where, even on the background of hypoglycemic drugs, the level of HbA1c was rather high (7.1±2.12; p<0.05).

There was a correlation between the OCI and the frequency (r=0.59; p<0.05), duration (r=0.58; p<0.05) and severity (r=0.53, p<0.05) of RS attacks. The highest values of the OCI were observed in the patients with a comorbidity and DM (95.2±5.2) and differed significantly from the values in RA patients with RS without DM (84.5±4.6; p<0.05) and those in RA patients without a comorbidity (66.3±3.5; p<0.05) (Table 2).

Table 1. Indicators of EDVBA, ET-1, TNF-α and CRP in the patients examined

Indicator	Control group, n=25	Group I: RA, n=38	Group II: RA + RS, n=47	
			IIa: RA+RS, n=32	IIb: RA+RS+DM, n=15
ED	-	29 (34.1%)	32 (37.65%)	15 (17.65%)
EDVBA, %	12.9±0.4	8.8±0.3*	6.5±0.2*•	6.1±0.2*•°’
ET-1, pg/ml	0.75±0.09	4.63±0.15*	6.01±0.46*•	9.17±0.63*•°’
TNF-α, pg/ml	24.55±1.13	57.9±1.6*	68.3±1.9*•	83.6±1.4*•°’
CRP, mg/l	3.9±0.71	23.89±1.77*	29.37±3.56*•	35.2±2.66*•°’
Blood glucose, mmol/l	4.51±0.25	5.05±0.14*•	5.9±0.5*•	8.72±1.61*•°’
HbA1c, mmol/l	4.7±0.21	5.7±0.4*•	5.8±0.2*•	7.1±2.12*•°’

*notes: n – number of patients; * - significance of difference from the control group p<0.05;*
• - significance of difference between the patients with RA and those with RA and co-existent RS, p<0.05;
° - significance of difference between the patients with RA and those with RA, co-existent RS and DM, p<0.05;
‘ - significance of difference between the patients with RA and co-existent RS and those with RA, co-existent RS and DM, p<0.05

Table 2. OCI, frequency, duration and severity of RS attacks in the patients with RA

Indicator	Control group, n=25	RA, n=38	RA +RS, n=47	
			RA + RS, n=32	RA + RS + DM, n=15
Frequency	-	3.7±0.5	6.7±0.5	7.8±0.5*°’
Duration, min.	-	12.8±2.1	23.7±3.6	24.7±3.6*°’
Severity, points	-	3.1±0.2	5.3±0.5	6.6±0.6*°’
OCI, %	54.3±3.5	66.3±3.5*	84.5±4.6*	95.2±5.2*°’

notes: n – number of patients;
** - significance of difference from the control group p<0.05;*
° - significance of difference between the patients with RA and those with RA and co-existent RS, p<0.05;
‹ - significance of difference between RA patients with RS and those with co-existent RS and DM, p<0.05

Clinical manifestations, features of the inflammatory process and changes in the indicators of endothelial function in RA patients with co-existent RS and DM are still poorly understood and require further study. In general, the results of our study are consistent with the literature. High levels of CRP, TNF-α and ET-1 in RA patients with co-existent RS were presented in national and international studies [4, 21]. Many authors, including Blahynina I.I., studied early ED development and the presence of high RF titers in patients with RA [6,12,16].

However, in our study, to objectively assess changes in the peripheral circulation, capillaroscopic examination of the patient was used. Nailfold capillaroscopy is a highly informative, fast and convenient method for diagnosing and monitoring RS progression in RA patients with DM. For the first time ever, we used the OCI for an objective assessment of changes in the peripheral circulation and demonstrated its high informative value in instrumental assessment of RS clinical course in RA patients with DM.

Conclusions

1. In the patients with secondary RS, the activity of RA inflamm - tory syndrome was higher as compared to RA patients without RS as evidenced by higher indicators of CRP and TNF-α in Group II.
2. Blood glucose level was significantly higher in RA patients with co-existent RS and DM as compared to the patients without RS.
3. Hypoglycemic therapy was less effective in the patients with a comorbidity as evidenced by high HbA1c levels in RA patients with secondary RS and DM.
4. In the patients with secondary RS and DM, ED severity and frequency were higher than those in RA patients with secondary RS without DM.
5. In the patients with RA, co-existent secondary RS and DM, high levels of ET-1 and the OCI, low indicators of EDVBA served as unfavorable prognostic signs of the clinical course of the disease.
6. A detailed study of the pathophysiological and immunological features of the clinical course of secondary RS will allow us to optimize its treatment schemes in patients with RA, reduce clinical and laboratory manifestation of RA and improve quality of life in such patients, especially those with a comorbidity.

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SUMMARY

COMORBID CONDITION – DIABETES MELLITUS WITH CO-EXISTENT RAYNAUD’S SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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The most common comorbidities in patients with rheumatic diseases include cardiovascular diseases (CVD), liver and biliary tract infection, lung diseases, amyloidosis, fractures of dif-

ferent localizations, malignant neoplasms, metabolic disorders and diabetes mellitus (DM).

The aim of study was to investigate the clinical course of DM and rheumatoid arthritis (RS) in patients with RA using laboratory and instrumental research methods.

There were examined 85 patients with RA who were treated in the rheumatology department of Ivano-Frankivsk Central City Clinical Hospital. The patients' age ranged from 40 to 70 years.

Endothelial dysfunction (ED) signs were observed in 76 (89.4%) patients. ED was diagnosed in all patients with RA, co-existent RS and DM. In the patients with RA and those with RA and co-existent RS, impaired EDVBA was detected. In the patients of Group II, the indicator of EDVBA (6.5±0.2%) was significantly lower as compared to the patients of Group I (8.8±0.3%) ($p<0.05$).

The levels of both CRP and TNF-α, serving as non-specific inflammatory markers, were significantly higher (29.37±3.56 mg/l, $p<0.01$) in the patients with RS as compared to the patients with RA only (23.89±1.77 mg/l).

A detailed study of the pathophysiological and immunological features of the clinical course of secondary RS will allow us to optimize its treatment schemes in patients with RA, reduce clinical and laboratory manifestation of RA and improve quality of life in such patients, especially those with a comorbidity.

Keywords: rheumatoid arthritis, Raynaud's syndrome, diabetes mellitus endothelial dysfunction.

РЕЗЮМЕ

КОМОРБИДНОЕ СОСТОЯНИЕ: САХАРНЫЙ ДИАБЕТ В СОЧЕТАНИИ С СИНДРОМОМ РЕЙНО У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

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Ключевым звеном патогенеза ревматоидного артрита (РА) с сахарным диабетом (СД) являются сложные дефекты Т-клеточной иммунорегуляции и В-клеточной толерантности, которые проявляются дисбалансом между продукцией провоспалительных и противовоспалительных цитокинов, вследствие чего возникает хронический системный воспалительный процесс.

Цель исследования - изучить уровень глюкозы крови и особенности течения сахарного диабета и синдрома Рейно у больных ревматоидным артритом.

Обследовано 85 больных (12 мужчин и 73 женщины) больных РА. Больные разделены на две группы: I группа (n=38) - больные РА II группа (n=47) - больные РА с вторичным СР и СД. Больные II группы разделены на 2 подгруппы II-а (n=32) - больные РА и вторичным СР); группу II-б (n=15) - больные РА и вторичным СР и СД, дополнительно принимавшие гипогликемизирующую терапию.

Признаки эндотелиальтнои дисфункции (ЭД) обнаружены у 76 (89,4%) обследованных. У всех больных РА в сочетании с вторичным СР и СД диагностирована ЭД. Установлено, что у больных РА и РА в сочетании с СР отмечается недостаточная эндотелийзависимая вазодилатация плечевой артерии (ЭЗВПА). У больных II группы показатель ЭЗВПА достоверно ($p<0,05$) ниже (6,5±0,2%) в сравнении с больными I группы (8,8±0,3%), что, по всей вероятности, обусловлено постоянными вазоспастическими атаками и приводит к нарушению целостности эндотелия.

Сравнение показателей ЭД у больных I и II групп выявило рост показателей глюкозы крови. У больных II-а подгруппы (без СД) уровень HbA1c составил 5,8±0,2, у пациентов II-б подгруппы - 7,1±2,12, что достоверно выше ($p<0,05$), чем у больных I группы (5,7±0,4).

Показатели глюкозы крови у пациентов с РА и вторичным СР без СД значительно выше, чем у пациентов без СР, как и у больных РА на фоне вторичного СР и СД, которые принимамали гипогликемизирующую терапию. Выраженность и частота ЭД у больных вторичным СР и СД выше, чем у пациентов с РА и вторичным СР без СД.

რეზიუმე

კომორბიდული მდგომარეობა: შაქრიანი დიაბეტი, შერწყმული რეინოს სინდრომთან რევმატოიდული ართრიტით დაავადებულებში

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ივანო-ფრანკოვსკის ეროვნული სამედიცინო უნივერსიტეტი

რევმატოიდული არტრიტის, შაქრიან დიაბეტთან ერთად, პათოგენეზის საკვანძო რგოლს წარმოადგენს Т-უჯრედული იმუნორეგულაციის და В-უჯრედული ტოლერანტობის რთული დეფექტები, რაც ვლინდება დისბალანსით პროანთებითი და ანთების საწინააღმდეგო ციტოკინების პროდუქციას შორის, რის შედეგადაც ქრონიკული სისტემური ანთებითი პროცესი ვითარდება.

კვლევის მიზანს წარმოადგენდა გლუკოზის დონის, შაქრიანი დიაბეტის და რეინოს სინდრომის მიმდინარეობის თავისებურებების შეფასება რევმატოიდული ართრიტით დაავადებულებში.

გამოკვლეულია 85 პაციენტი (12 მამაკაცი, 73 ქალი) რევმატოიდული ართრიტით. პაციენტები დაიყო ორ ჯგუფად: I ჯგუფი (n=38) - პაციენტები რევმატოიდული ართრიტით, II ჯგუფი (n=47) - პაციენტები რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით და შაქრიანი დიაბეტით.

II ჯგუფის პაციენტები დაიყო ორ ქვეჯგუფად: ქვეჯგუფი II-ა (n=32) - პაციენტები რევმატოიდული ართრიტით და მეორადი რეინოს სინდრომით; ქვეჯგუფი II-ბ (n=15) – პაციენტები რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით და შაქრიანი დიაბეტით, რომელნიც დამატებით იღებდნენ ჰიპოგლიკემიურ მკურნალობას.

ენდოთელური დისფუნქციის ნიშნები გამოვლინდა 76 (89,4%) პაციენტში. ყველა პაციენტში რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით და შაქრიანი დიაბეტით დიაგნოსტირდა ენდოთელური დისფუნქცია. დადგენილია, რომ პაციენტებში რევმატოიდული ართრიტით და პაციენტებში რევმატოიდული ართრიტით რეინოს სინდრომთან ერთად აღინიშნება არასაკმარისი მხრის არტერიის ენდოთელიუმდამოკიდებული ვაზოდილატაცია. II ჯგუფის პაციენტებში მხრის არტერიის ენდოთელიუმდამოკიდებული ვაზოდილატაციის მაჩვენებელი სარწმუნოდ

(p<0,05) ნაკლებია (6,5±0,2%), I ჯგუფის პაციენტებთან შედარებით (8,8±0,3%), რაც, დიდი ალბათობით, განპირობებულია მუდმივი ვაზოსპასტიური შეტევებით და იწვევს ენდოთელიუმის მთლიანობის დარღვევას.

ენდოთელური დისფუნქციის მაჩვენებლების შედარებით I და II ჯგუფის პაციენტებს შორის გამოვლინდა გლუკოზის მაჩვენებლების ზრდა. II-ა ქვეჯგუფის პაციენტებში (შაქრიანი დიაბეტის გარეშე) HbA1-ის დონემ შეადგინა 5,8±0,2 , II-ბ ქვეჯგუფის პაციენტებში - 7,1±2,12, რაც სარწმუნოდ (p<0,05) მაღალია, ვიდრე I ჯგუფის პაციენტებში (5,7±0,4).

გლუკოზის მაჩვენებლები პაციენტებში რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით შაქრიანი დიაბეტის გარეშე მნიშვნელოვნად მაღალია, ვიდრე პაციენტებში რეინოს სინდრომის გარეშე, ისევე, როგორც პაციენტებში რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით და შაქრიანი დიაბეტით, რომელნიც იტარებდნენ ჰიპოგლიკემიურ თერაპიას. ენდოთელური დისფუნქციის გამოხატვის ხარისხი და სიხშირე პაციენტებში მეორადი რეინოს სინდრომით და შაქრიანი დიაბეტით უფრო მაღალია, ვიდრე პაციენტებში რევმატოიდული ართრიტით, მეორადი რეინოს სინდრომით შაქრიანი დიაბეტის გარეშე.

RENAL, HEPATIC AND IMMUNE FUNCTION INDICES IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy is an X linked genetic disorder, which mainly affects boys. The incidence of the disease is one in three-five thousand newborns. The disease is severe; patients usually die before reaching 20-25 years old. Its onset is caused by mutations in the dystrophin gene [2,11-13,17].

Today, the DMD gene is known to contain 79 exons, encoding 3685 amino acids (protein of molecular weight about 427 kDa). Dystrophin has four main functional domains that together make actin cytoskeleton to be associated with the extracellular matrix and provide stability and strength to muscle fibers [4-6,9,18]. The dystrophin gene can form several tissue-specific forms of different molecular weights, each of which is operated by a certain promoter. There are four complete dystrophin proteins of high molecular weight about 427 kDa, i.e. M-dystrophin (Dp427 m), which is presented in skeletal and smooth muscles; C-dystrophin (Dp427c), presented in the cerebral cortex and hippocampus; P-dystrophin (Dp427p), presented in Purkinje cells; L-dystrophin (Dp427l), presented in lymphocytes. There are also alternative promoters, expressing 5 non-muscular dystrophin protein isoforms: Dp260, which is presented in Dp140 retina, expressed in the central nervous system and kidneys, Dp116, which is found in Schwann cells, Dp71, distributed in the brain, the deficit of which correlates with the severity of mental retardation in case of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) [3,7,8,10,19]. Taking into account such a diversity in dystrophin protein isoforms distribution in various organs and tissues, in particular in the nervous system and kidneys, as well as in cells that provide immune function (namely, in lymphocytes), we decided to enlarge upon renal, hepatic and immune function indices in patients with Duchenne muscular dystrophy (MDD) [1,14-16].

The purpose of the study is to examine in depth and analyze renal, hepatic and immune function indices in patients with Duchenne muscular dystrophy.

Material and methods. We analyzed the follow up clinical and laboratory data of Duchenne muscular dystrophy in 32 patients. The patients underwent a standardized examination, involving studying the medical case history, general clinical data, determining Sheldon's somatotype and the constitutional type, the detailed neurological status examination, testing a personality type, laboratory and instrumental examinations.

Through the laboratory examination we determined the general blood test indicators, total serum protein levels, total cholesterol, the ALAT, ASAT, CPK levels, creatinine and urea blood levels, glomerular filtration rate (GFR), the immunogram indices (dynamic data (B-lymphocytes (CD19/CD45), %; T-lymphocytes (CD3/CD 45), %; T-helpers (CD3/CD45/CD4), %; T-suppressors (CD3/CD45/CD8), %; CD4:CD8 ratio; natural killer cells ratio, myositis profile (Mi-2, IgG antibodies (idiopathic myositis marker); Ku, IgG antibodies (sclerodermia and myositis combination marker); the PM-Scl complex, IgG antibodies (sclerodermia marker); histidyl tRNA synthetase (Jo-1), IgG antibodies; threonyl-tRNA synthetase (PL-7), IgG antibodies; alanyl-tRNA synthetase (PL-12), IgG antibodies; RING-type E3 ubiquitin-ligase (Ro-52), IgG antibodies and the genetic markers of the disease.

The instrumental examination included the ultrasound of the abdominal organs, muscles, as well as echo-cardiography, electroneuromyography.

Results and discussion. When analyzing the immunograms of patients with muscular dystrophy, we followed-up the following parameters: B-lymphocytes (CD19/CD45), %; T-lymphocytes (CD3/CD 45), %; T-helpers (CD3/CD45/CD4), %; T-suppressors (CD3/CD45/CD8); CD4:CD8 ratio; natural killer cells ratio.

The T-lymphocytes (CD3/CD45) count was found to be not within the reference values in only 4 (8%) cases among 31 patients with muscular dystrophy, examined by us, namely: in 3 (9.7%) cases it was above 86% and in 1 case (3.2%) it was below 56% (Fig. 1).

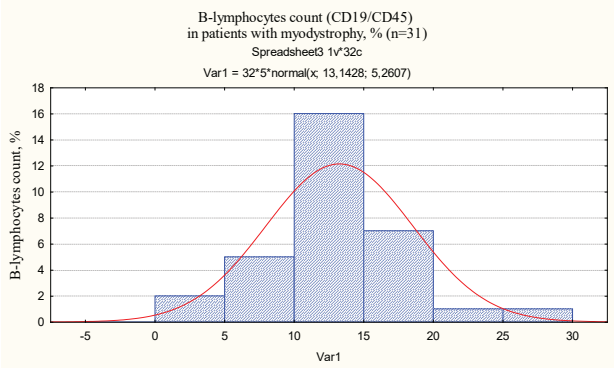

Fig. 1. B-lymphocytes count (CD19/CD45) in patients with muscular dystrophy

Among 31 patients with muscular dystrophy, examined by us, the T-lymphocytes (CD3/ CD45) count was observed to be below the normal range in 8 (25,8%) cases, and to be within the reference values in 23 (74,2%) cases (Fig. 2).

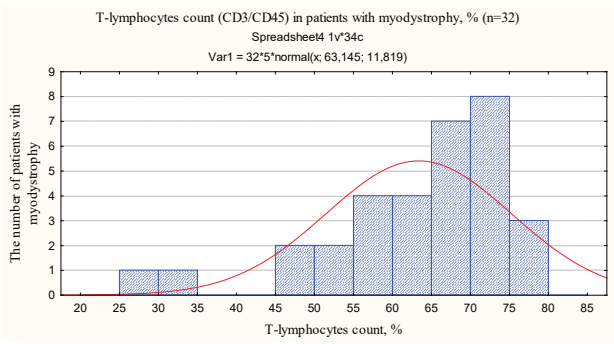

Fig. 2. T-lymphocytes count (CD3/CD45) in patients with muscular dystrophy

Among 31 patients with muscular dystrophy, examined by us, T-helpers (CD3/CD45/CD4) count was found to be lower than the reference values in 14 (45.2%) patients, and to be within the normal limits in 17 (54.8%) patients (Fig. 3).

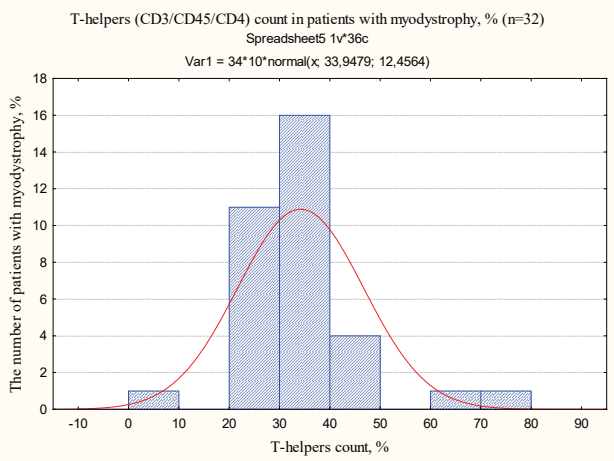

Fig. 3. T-helpers (CD3/CD45/CD4) count in patients with muscular dystrophy

Among 31 patients with muscular dystrophy, examined by us, T-suppressors (CD3/ CD45/ CD8) count was found to be within the reference values in the vast majority of cases (28 patients, i. e. 90,3%). Furthermore, the count of the index was above the reference values in 3 (9,7%) cases (Fig. 4).

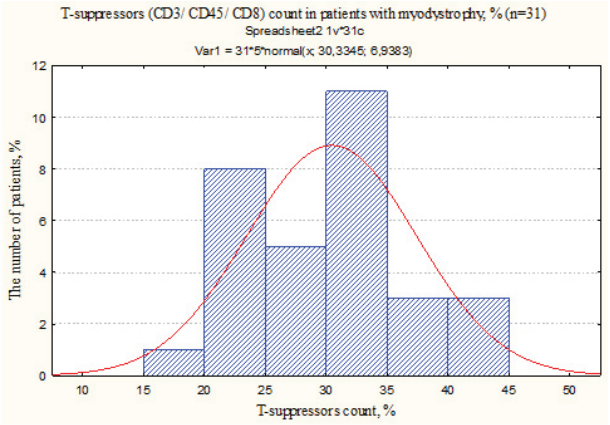

Fig. 4. T-suppressors (CD3/ CD45/ CD8) count in patients with muscular dystrophy

Among 31 patients with muscular dystrophy, examined by us, the CD4:CD8 ratio was observed to be lower than the reference values in 10 (32,3%) patients (Fig. 5).

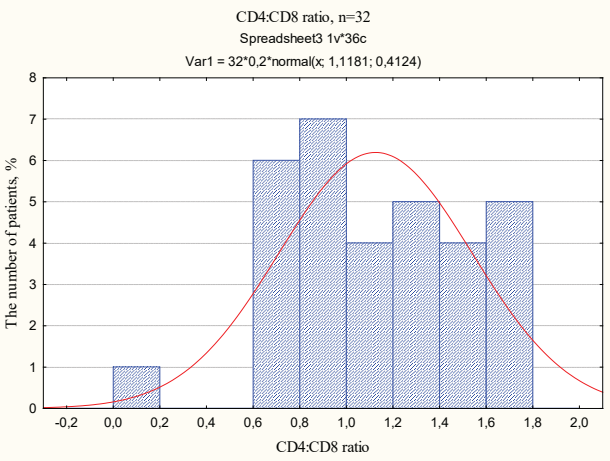

Fig. 5. CD4:CD8 ratio in patients with muscular dystrophy

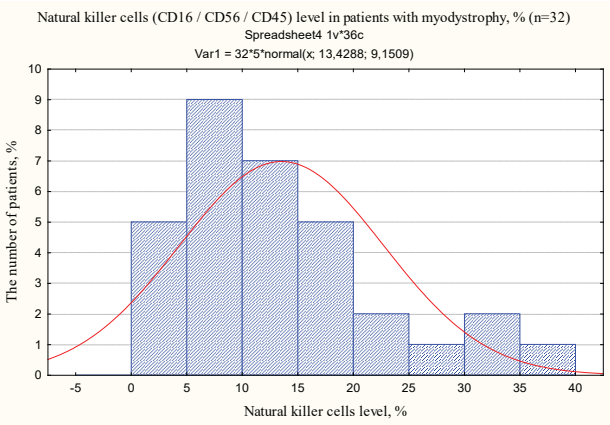

Fig. 6. Natural killer cells (CD16/CD56/CD45) level in patients with muscular dystrophy

Among 31 patients with muscular dystrophy, examined by us, the natural killer cells (CD16 / CD56 / CD45) level was found to

be within the reference values in the vast majority of cases (23 patients, i. e. 74,2%). Furthermore, the count of the index was below the reference values in 3 (9,7%) cases (Fig. 6).

The correlation coefficien between the B-lymphocytes count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to - 0.42, suggesting the presence of an indirect moderate correlation between the mentioned phenomena (p<0.05). The correlations are presented in Fig.7.

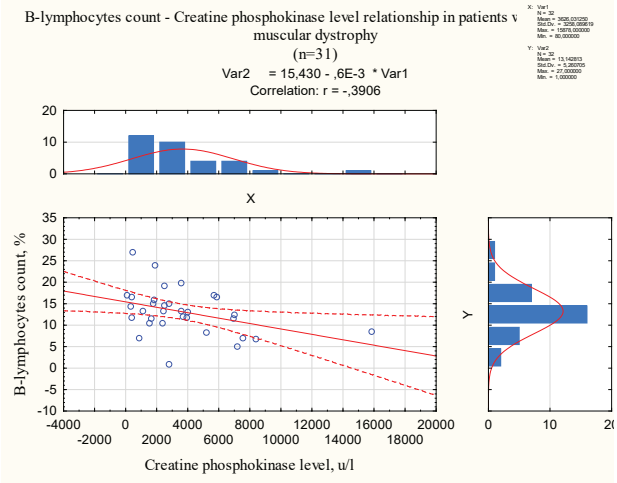

Fig. 7. B-lymphocytes count – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between the T-lymphocytes count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to -0.1, no correlation between the mentioned phenomena was found (p<0.05). The correlations are presented in Fig.8.

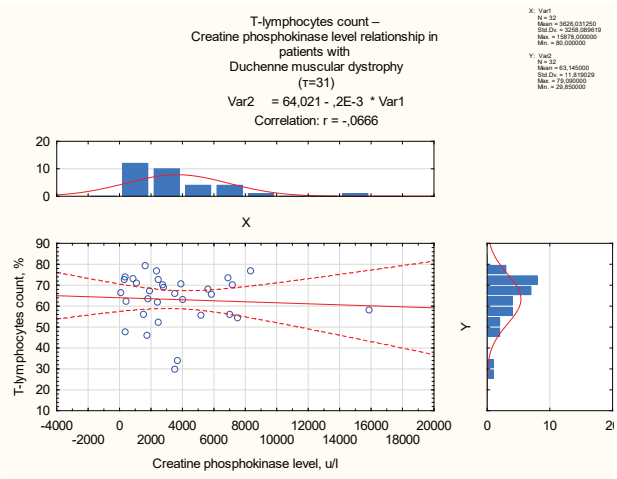

Fig. 8. T-lymphocytes count – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between the T-helpers count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to +0.1, no correlation between the mentioned phenomena was found (p<0.05). The correlations are presented in Fig. 9.

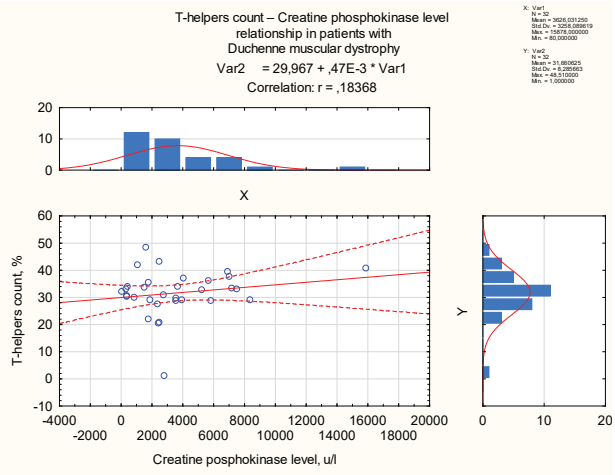

Fig. 9. T-helpers count – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between the T-suppressors count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to +0.01, no correlation between the mentioned phenomena was found (p<0.05). The correlations are presented in Fig. 10.

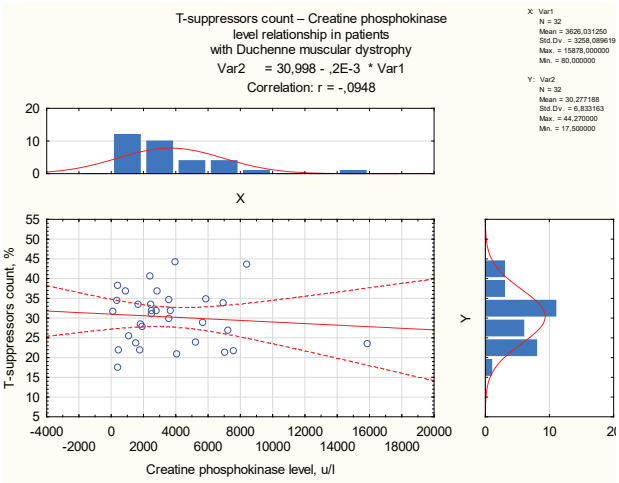

Fig. 10. T-suppressors count – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between the natural killer cells count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to +0.1, no correlation between the mentioned phenomena was found (p<0.05). The correlations are presented in Fig. 11.

The correlation coefficien between the onset age of Duchenne muscular dystrophy and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to - 0.3, suggesting the presence of an indirect weak correlation between the mentioned phenomena (p<0.05). The correlations are presented in Fig. 12.

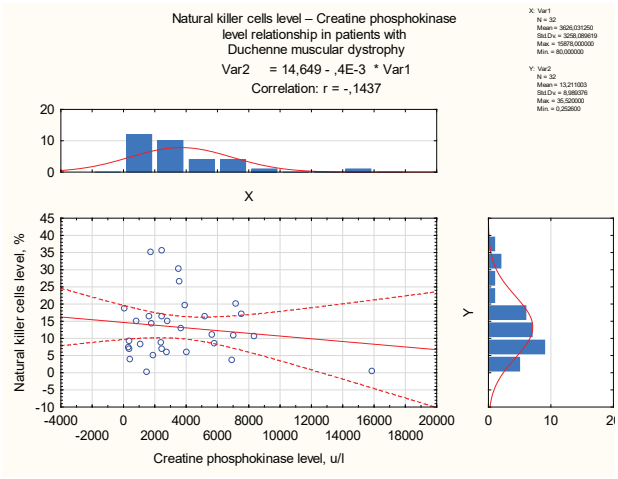

Fig. 11. Natural killer cells level – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

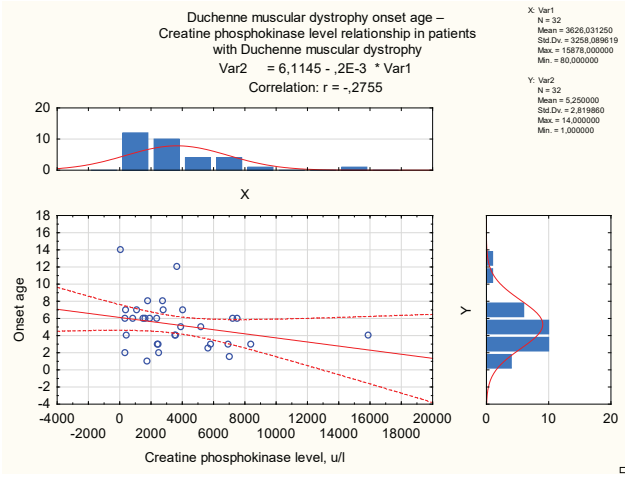

Fig. 12. Duchenne muscular dystrophy onset age – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between Helper-suppressor cell ratio and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to +0.22, no correlation between the mentioned phenomena was found ($p<0.05$). The correlations are presented in Fig. 13.

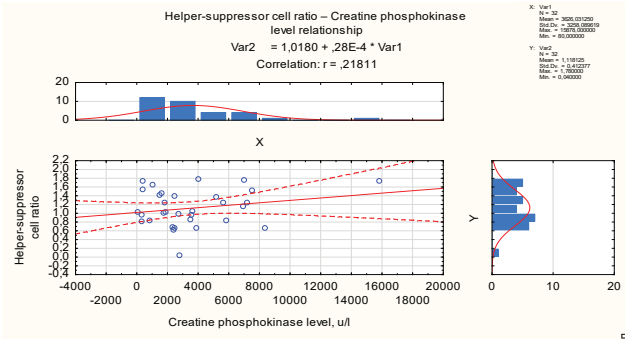

Fig. 13. Helper-suppressor cell ratio – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

Having analyzed the renal function indices in patients with Duchenne muscular dystrophy, we revealed serum urea level to be within the age-related reference values in the vast majority of cases, and it was above the norm only in 3.1% of cases. Moreover, the creatinine blood level was lower than the lower limit of the reference values in almost a third of patients (21%). When determining the glomerular filtration rate (GFR) by the SKD-EPI formula, we found it to be insignificantly reduced in 16% of patients, and it was within 66-87 ml/min/1.73 m^2.

The correlation coefficien between serum urea level and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to - 0.28, suggesting the presence of an indirect weak correlation between the mentioned phenomena ($p<0.05$). The correlations are presented in Fig. 14.

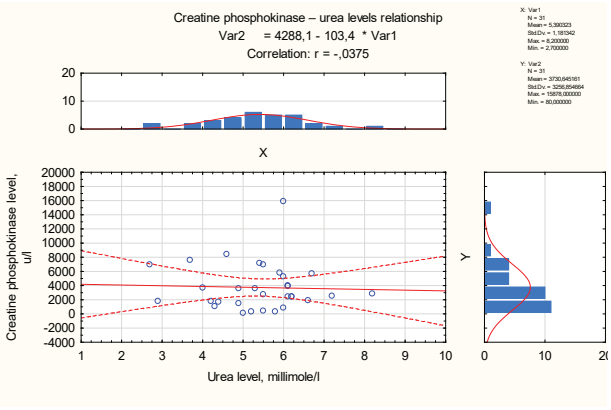

Fig. 14. Duchenne muscular dystrophy onset age – Creatine phosphokinase level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between Creatine phosphokinase level and creatinine blood level in patients with Duchenne muscular dystrophy was equal to - 0.22, no correlation between the mentioned phenomena was found ($p<0.05$). The correlations are presented in Fig. 15.

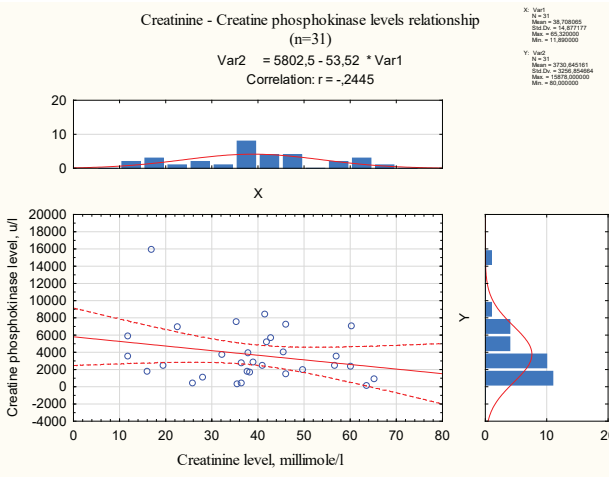

Fig. 15. Creatine phosphokinase level – creatinine blood level relationship in patients with Duchenne muscular dystrophy

The correlation coefficien between Creatine phosphokinase level and the glomerular filtration rate in patients with Duchenne muscular dystrophy was equal to +0,16, no correlation between the mentioned phenomena was found. The correlations are presented in Fig. 16.

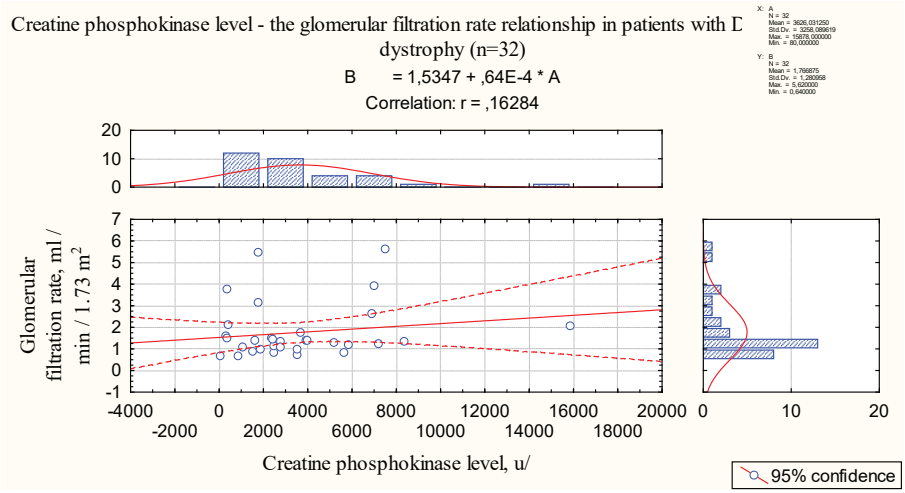

Fig. 16. Creatine phosphokinase level – the glomerular filtration rate relationship in patients with Duchenne muscular dystrophy

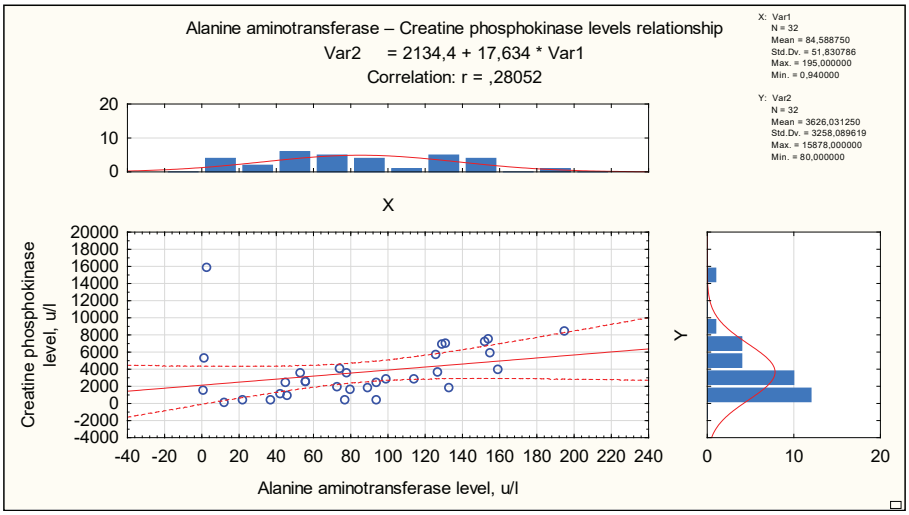

Fig. 17. Creatine phosphokinase level – alanine aminotransferase level relationship in patients with Duchenne muscular dystrophy

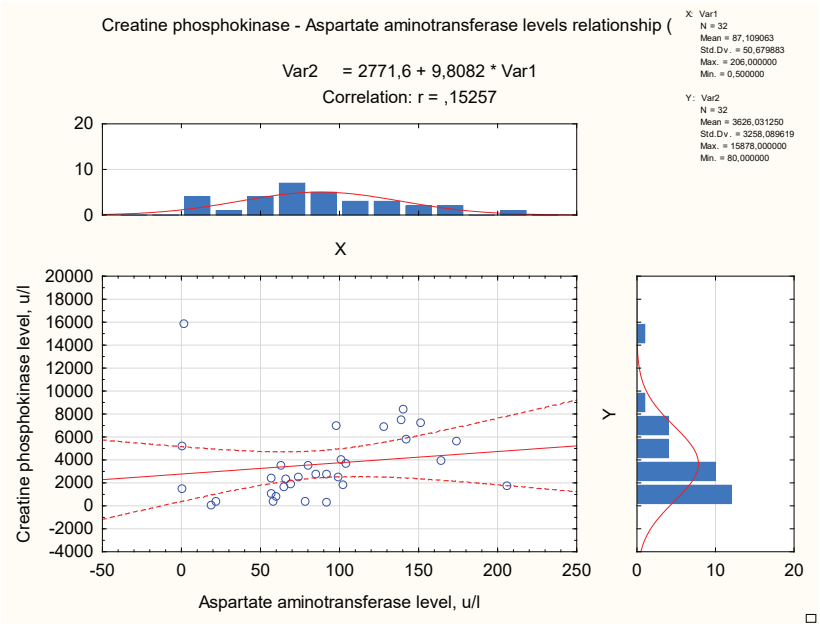

Fig. 18. Creatine phosphokinase level – aspartate aminotransferase level relationship in patients with Duchenne muscular dystrophy

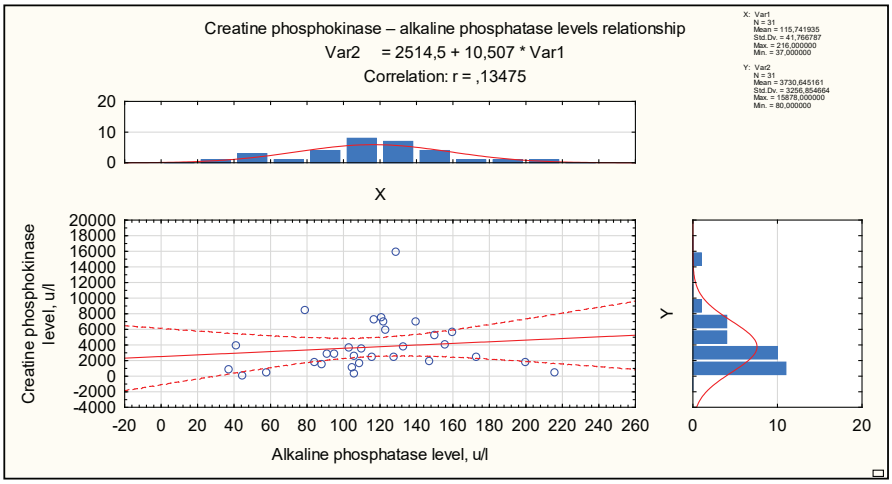

Fig. 19. Creatine phosphokinase level – alkaline phosphatase level relationship in patients with Duchenne muscular dystrophy

Having analyzed the hepatic function indices, we revealed that such indicators of liver enzymatic activity as alanine aminotransferase (ALA) and aspartate aminotransferase (AsAt) were significantly over the limit in almost all the patients (94%) with Duchenne muscular dystrophy.

The correlation coefficie–n between Creatine phosphokinase level and the alanine aminotransferase level in patients with Duchenne muscular dystrophy was equal to +0,86, suggesting the presence of a direct strong correlation between the mentioned phenomena. The correlations are presented in Fig. 17.

The correlation coefficien between aspartate aminotransferase (AsAt) and Creatine phosphokinase level in patients with Duchenne muscular dystrophy was equal to +0,56, suggesting the presence of a direct moderate correlation between the mentioned phenomena. The correlations are presented in Fig. 18.

In our study, we also found that the level of alkaline phosphatase was also significantly higher than the normal one in 69% of our patients.

The correlation coefficien between Creatine phosphokinase level and alkaline phosphatase level in patients with Duchenne muscular dystrophy was equal to +0,14, no correlation between the mentioned phenomena was found. The correlations are presented in Fig. 19.

According to the analysis of the immunograms, the T-helpers level was found to be below the reference value in 14 (45,2%) patients. Herewith, the B-lymphocytes count was observed to deviate from the norm in only 4 patients (8%).

However, there was established the presence of an indirect moderate correlation between the B-lymphocytes count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy; the correlation coefficient was equal to - 0.42 ($p<0,05$

Having analyzed the renal function indices, we revealed that the creatinine blood level was lower than the lower limit of the reference values in almost a third of patients (21%), but the glomerular filtration rate (GFR) by the SKD-EPI formula was found to be insignificantly reduced in 16% of patients, and it was within 66-87 ml / min/1.73 m^2.

Regardless, no correlation between the Creatine phosphokinase level, on one side, and creatinine blood level and the glomerular filtration rate, on the other side, was found. However, there was established the presence of an indirect weak correlation between the Creatine phosphokinase level and serum urea level in patients with Duchenne muscular dystrophy (the correlation coefficient was equal to - 0.28, $p<0.05$)

Having analyzed the hepatic function indices, we revealed that such indicators of liver enzymatic activity as alanine aminotransferase and aspartate aminotransferase were significantly over the limit in almost all the patients (94%) with Duchenne muscular dystrophy. Concurrently, we revealed the presence of a direct strong correlation between the Creatine phosphokinase level and the alanine aminotransferase level, which was equal to +0,86 ($p<0,05$) and the presence of a direct moderate correlation between the aspartate aminotransferase and the Creatine phosphokinase level which was equal to + 0.56 ($p<0,05$).

We also found that the level of alkaline phosphatase was also significantly higher than the normal one in 69% of our patients

Conclusions.

1. The patients with Duchenne muscular dystrophy were found to have deviations in the indices of immune status, in particular, the T-helpers level was below normal in almost half of the examined patients. There was also observed a correlation between the B-lymphocytes count and the Creatine phosphokinase level.

2. The patients' renal dysfunction was characterized by the following: 21% of our patients were registered to have a reduced creatinine blood level, and 16% of patients were registered to have a reduced glomerular filtration rate

3. The most deviations were registered in the indices of liver enzymatic activity in the patients with Duchenne muscular dystrophy. 94% of patients were revealed to have the increased alanine aminotransferase and aspartate aminotransferase levels, suggesting the presence of direct correlation (the strong and moderate ones, accordingly) between the indices and the Creatine phosphokinase level.

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SUMMARY

RENAL, HEPATIC AND IMMUNE FUNCTION INDICES IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

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The purpose of the study is to examine in depth and analyze renal, hepatic and immune function indices in patients with Duchenne muscular dystrophy. We analyzed the follow up clinical and laboratory data of Duchenne muscular dystrophy in 32 patients. The patients underwent a standardized examination, involving studying the medical case history, general clinical data, determining Sheldon's somatotype and the constitutional type, the detailed neurological status examination, testing a personality type, laboratory and instrumental examinations.

Through the laboratory examination we determined the general blood test indicators, total serum protein levels, total cholesterol, the ALAT, ASAT, CPK levels, creatinine and urea blood levels, glomerular filtration rate (GFR), the immunogram indices (dynamic data (B-lymphocytes (CD19/CD45), %; T-lymphocytes (CD3/CD 45), %; T-helpers (CD3/CD45/CD4), %; T-suppressors (CD3/CD45/ CD8), %; CD4:CD8 ratio; natural killer cells ratio, myositis profile (Mi-2, IgG antibodies (idiopathic myositis marker); Ku, IgG antibodies (sclerodermia and myositis combination marker); the PM-Scl complex, IgG antibodies (sclerodermia marker); histidyl tRNA synthetase (Jo-1), IgG antibodies; threonyl-tRNA synthetase (PL-7), IgG antibodies; alanyl-tRNA synthetase (PL-12), IgG antibodies; RING-type E3 ubiquitin-ligase (Ro-52), IgG antibodies and the genetic markers of the disease.

The instrumental examination included the ultrasound of the abdominal organs, muscles, as well as echo-cardiography, electroneuromyography.

According to the analysis of the immunograms, the T-helpers level was found to be below the reference value in 14 patients (45,2%).

Herewith, the B-lymphocytes count was observed to deviate from the norm in only 4 patients (8%).

However, there was established the presence of an indirect moderate correlation between the B-lymphocytes count and Creatine phosphokinase level in patients with Duchenne muscular dystrophy; the correlation coefficien was equal to - 0.42 ($p<0,05$).

Having analyzed the renal function indices, we revealed that the creatinine blood level was lower than the lower limit of the reference values in almost a third of patients (21%), but the glomerular filtration rate (GFR) by the SKD-EPI formula was found to be insignificantly reduced in 16% of patients, and it was within 66-87 ml/min/1.73 m^2.

Regardless, no correlation between the Creatine phosphokinase level, on one side, and creatinine blood level and the glomerular filtration rate, on the other side, was found. However, there was established the presence of an indirect weak correlation between the Creatine phosphokinase level and serum urea level in patients with Duchenne muscular dystrophy (the correlation coefficient was equal to - 0.28, $p<0.05$)

Having analyzed the hepatic function indices, we revealed that such indicators of liver enzymatic activity as alanine aminotransferase and aspartate aminotransferase were significantly over the limit in almost all the patients (94%) with Duchenne muscular dystrophy. Concurrently, we revealed the presence of a direct strong correlation between the Creatine phosphokinase level and the alanine aminotransferase level, which was equal to +0,86 ($p<0,05$) and the presence of a direct moderate correlation between the aspartate aminotransferase and the Creatine phosphokinase level which was equal to + 0.56 ($p<0,05$).

We also found that the level of alkaline phosphatase was also significantly higher than the normal one in 69% of our patients

The patients with Duchenne muscular dystrophy had various multidirectional disorders of the immune status, impaired renal function (in particular, a decrease in serum creatinine concentra-

tion and reduced glomerular filtrat on rate), as well as the divergence of liver enzyme parameters (in particular, a significant increase in transaminase levels).

Keywords: Duchenne muscular dystrophy, renal indices, hepatic indices, immune function indices.

РЕЗЮМЕ

ПОКАЗАТЕЛИ ФУНКЦИИ ПОЧЕК, ПЕЧЕНИ И ИММУННОЙ СИСТЕМЫ У ПАЦИЕНТОВ С МИОДИСТРОФИЕЙ ДЮШЕННА

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Цель исследования - анализ показателей функции почек, печени и иммунной системы у пациентов с миодистрофией Дюшенна.

Проанализированы клинические и лабораторные данные 32 пациентов с миодистрофией Дюшенна. Пациенты прошли стандартизированный комплекс обследования: подробное изучение анамнеза, данные общеклинического обследования, определение соматотипа по Шелдону и конституционального типа, детализированное исследование неврологического статуса, проведение теста определения психотипа личности, лабораторное и инструментальное обследование. При лабораторном обследовании определяли: показатели общего анализа крови, уровни общего белка, мочевины, креатинина в сыворотке крови, скорости клубочковой фильтрации (СКФ), общего холестерина, аланинаминотрансферазы, аспартатаминотрансферазы, креатинфосфокиназы (КФК), показатели иммунограммы (В-лимфоциты; Т-лимфоциты; Т-хелперы; Т-супрессоры; хелперно-супрессорное соотношение; NK-натуральные киллеры), миозитного профиля (комплекс PM-Scl, антитела IgG (маркер склеродермии); гистидил-т-РНК синтетаза (Jo-1), антитела IgG; треонил-т-РНК синтетаза (PL-7), антитела IgG; аланил-т-РНК синтетаза (PL-12), антитела IgG; RING зависимая Е3 лигаза (Ro-52), антитела IgG), а также генетические маркеры заболевания. Инструментальные методы включали ультразвуковое исследование органов брюшной полости и мышц, эхокардиографию, электронейромиографию.

Анализ параметров иммунного статуса выявил: у 14 (45,2%) пациентов уровень Т-хелперов ниже референтных значений, у 4 (8%) пациентов отклонение уровня В-лимфоцитов от нормы. Установлено наличие обратной средней силы связи между уровнем В-лимфоцитов и уровнем креатинфосфокиназы у пациентов с миодистрофией Дюшенна, коэффициент корреляции (КК)=-0.42 ($p<0,05$).

Исследование параметров почечной функции показало: уровень креатинина сыворотки крови у 7 (21%) пациентов был ниже, чем нижняя граница референтных значений, уровень СКФ по формуле CKD-EPI у 5 (16%) пациентов был незначительно ниже, находясь в диапазоне значений 66-87 мл/мин/1.73 м^2. Никаких корреляционных взаимосвязей между уровнем КФК и уровнем креатинина в сыворотке крови, а также уровнем СКФ не установлено. Обнаружена слабая обратная связь между показателями уровня КФК и мочевины в сыворотке крови у пациентов с миодистрофией Дюшенна (КК=-0.28, $p<0,05$).

Анализ параметров функции печени выявил, что у 30 (94%) пациентов с миодистрофией Дюшенна показатели уровня ферментативной функции печени (аланинаминотрансфераза и аспартатаминотрансфераза) значительно превышали норму. Установлено наличие прямой сильной связи между уровнями КФК и уровнем аланинаминотрансферазы в сыворотке крови (КК=+0.86, $p<0,05$) и прямой средней силы связи между уровнями аспартатаминотрансферазы и КФК (КК=+0.56, $p<0,05$).

Установлено, что у 22 (69%) обследованных пациентов уровень щелочной фосфатазы значительно превышал нормальные значения.

Авторы заключают, что у пациентов с миодистрофией Дюшенна отмечаются различные разнонаправленные нарушения иммунного статуса, отклонение почечных параметров, в частности снижение уровня сывороточного креатинина и скорости клубочковой фильтрации и параметров печеночных ферментов, в частности значительное повышение уровня трансаминаз.

რეზიუმე

თირკმლის, ღვიძლის და იმუნური სისტემის ფუნქციის მაჩვენებლები პაციენტებში დიუშენის მიოდისტროფიით

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კვლევის მიზანს წარმოადგენდა თირკმლის, ღვიძლის და იმუნური სისტემის ფუნქციის მაჩვენებლების ანალიზი პაციენტებში დიუშენის მიოდისტროფიით.

გაანალიზებულია დიუშენის მიოდისტროფიის მქონე 32 პაციენტის კლინიკური და ლაბორატორიული მონაცემები. პაციენტებს ჩაუტარდა გამოკვლევის სტანდარტული კომპლექსი: ანამნეზის დაწვრილებითი შესწავლა, საერთო კლინიკური კვლევები, სომატოტიპის განსაზღვრა შელდონის მიხედვით და კონსტიტუციური ტიპის განსაზღვრა, ნევროლოგიური სტატუსის დეტალური კვლევა, ტესტი პიროვნების ფსიქოტიპის განსაზღვრისათვის, ლაბორატორიული და ინსტრუმენტული კვლევები. ლაბორატორიული კვლევისათვის განისაზღვრა: სისხლის საერთო ანალიზი, საერთო ცილა, შარდოვანა, კრეატინინის დონე სისხლის შრატში, გორგლოვანი ფილტრაციის სიჩქარე, საერთო ქოლესტერინი, ალანინამინოტრასფერაზა, ასპარტატამინიოტრანსფერაზა, კრეატინფოსფატაზა, იმუნოგრამის მაჩვენებლები, ასევე, დაავადების გენეტიკური მარკერები. ინსტრუმენტული მეთოდები მოიცავდა მუცლის ღრუს ორგანოების და კუნთების ულტრაბგერით კვლევას, ექოკარდიოგრაფიას, ელექტრონეირომიოგრაფიას.

ავტორები დაასკვნიან, რომ პაციენტებში დიუშენის მიოდისტროფიით აღინიშნება იმუნური სტატუსის, თირკმლის პარამეტრების (კერძოდ, შრატის კრეატინინის დონის და გორგლოვანი ფილტრაციის სიჩქარის შემცირება) და ღვიძლის ფერმენტების (კერძოდ, ტრანსამინაზების დონის მნიშვნელოვანი მომატება) განსხვავებული დარღვევები.

COMPLIANCE OF INITIALLY PRESCRIBED ANTI-TUBERCULOSIS TREATMENT REGIMENS WITH COMPLETE DRUG SUSCEPTIBILITY TEST RESULTS AND ITS ASSOCIATION WITH TREATMENT OUTCOMES IN GEORGIA (2015-2020)

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Tuberculosis continues to be a public health crisis for whole world. Globally, an estimated 10.0 million people fell ill with TB in 2018. The burden of disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, with the global average being around 130. There were an estimated 1.2 million TB deaths among HIV-negative people in 2018 and an additional 251 000 deaths among HIV positive people. TB affects people of both sexes in all age groups but the highest burden is in men (aged ≥15 years), who accounted for 57% of all TB cases in 2018. By comparison, women accounted for 32% and children (aged <15 years) for 11%. Drug-resistant TB continues to be a public health threat. In 2018, there were about half a million new cases of rifampicin-resistant TB (of which 78% had multidrug resistant TB [1].

According to the World Health Organization (WHO), in 2018, the total number of notified TB Cases in Georgia was 2 590 (incidence – 65 cases per 100 000 population). MDR-TB was diagnosed in 12% of new, and in 31% of previously treated cases. The treatment outcome was defined as successful in 84% of new and relapse cases registered in 2017 (cohort - 2351), in 65% of MDR/RR-TB and in 56% of XDR-TB cases started on second-line treatment in 2016 (cohorts – 339 and 55, respectively) [2].

In line with WHO recommendations, the Georgian algorithm for TB diagnosis recommends the GeneXpert MTB/RIF test and the line probe assays (LPAs) as the initial diagnostic tests for TB [3,4]. These rapid molecular genotypic drug susceptibility tests (gDSTs) can identify susceptibility to the one or two (Rifampicine or Isoniazid) key drugs out of four first-line anti-TB drugs which should be used in the DS-TB treatment regimens. The complete DST profile, such as susceptibility to all drugs, which may be included in the TB regimen, requires phenotypic DST (pDST), the results of which become available only two months after treatment initiation. Within this period only real DS-TB cases receives appropriate treatment. TB patients, who based on gDST started DS-TB treatment, but based on pDST are diagnosed as mono-, poly- or even as MDR- or XDR-TB cases, before pDST results are treated with first line drugs inappropriately.

A meta-analysis of previous studies shows that inaccurate DST by comparison to a reference standard led to under treatment of drug resistant tuberculosis and increased mortality. Rapid molecular DST of first- and second-line drugs at diagnosis is required to improve outcomes in patients with MDR-TB and pre-XDR/XDR-TB [5]. Comprehensive drug susceptibility testing (phenotypic and/or genotypic) is necessary to inform physicians about the best drugs to treat individual patients with tailor-made treatment regimens. Phenotypic drug resistance can now often, but with variable sensitivity, be predicted by molecular drug susceptibility testing based on e.g. whole genome sequencing (WGS), which in the future could become an affor - able method for the guidance of treatment decisions, especially in high-burden/resource-limited settings [6]. Although commercial genotypic drug-susceptibility tests (DST) are close to the goal, they are still not able to detect all relevant DR-TB related mutations. WGS allows better comprehension of DR-TB with a great discriminatory power; it's able to provide all the relevant information about M. tuberculosis drug susceptibility in a single test; and also can detect a mutation in rpoB which is not covered by commercial genotypic DST [8]. Although, the WGS of *Mycobacterium tuberculosis* is rapidly progressed from a research tool to a clinical application for the diagnosis and management of tuberculosis [9], it's still not available for programmatic use in Georgia.

Currently available gDSTs and pDST in Georgia gives opportunity to identify susceptibility to the key anti-TB drugs in majority of cases. In 2019, 99% of bacteriologically confirmed new and 93% of previously treated TB cases were tested for rifampicin resistance; and 242 MDR/RR-TB cases were tested for resistance to any fluoroquinolone [2], but the rate of resistance to the other drugs, the proportion of initially registered DS-TB cases who in period between of gDST and pDST results receives treatment that is fully compliant with the individual DST profile and whether this compliance is associated with the treatment outcomes, was not assessed. A recent study was designed to determine these important data.

Material and methods. A retrospective cohort study was conducted with individual data of >18 years old patients who were registered in the National Tuberculosis Electronic Register as the DS-TB cases from 2015 to 2020, whose DST profile was known and for whom the treatment outcome was defined until August 2020.Considering the inclusion criteria, 8468 patients, initially registered as DS-TB cases (n=1877[2015 cohort] + n=1891[2016 cohort] + n=1710[2017 cohort] + n=1526[2018 cohort] + n=1399[2019 cohort] + n=65[2020 cohort]), with known DST and treatment outcomes were selected as study participants.

The study was conducted at the National Center for Tuberculosis and Lung Disease as part of the Georgian National Tuberculosis Programme.

During the study period TB laboratory networks in Georgia performed smear microscopy, Xpert MTB/RIF testing, culture on solid and liquid media, DST to the first- and second-line drugs by automated Mycobacteria Growth Indicator Tube (MGIT) and LPA methods.

The country uses a standardized electronic TB recording and reporting system. Case classification and definition of treatment category is provided using specialized TB surveillance services in line with the latest WHO recommendations [10].

Data variables were collected in relation to study objectives and included socio-demographic characteristics, laboratory data, data of drug susceptibility tests results and treatment outcomes. The primary outcome was appropriateness of treatment defined as full compliance of prescribed regimens with gDST and pDST results, compared to inappropriate treatment regimens, which before pDST results included resistant drug(s). TB treatment outcomes were categorized as successful (Cured and completed) or unsuccessful (Failure, Death, Lost to follow-up, Moved to category 4, Transfer out or Not evaluated).

The data collected were analyzed by using of EasyStat (https://easystat.app). A descriptive analysis was performed for

socio-demographic, behavioral and clinical characteristics. Bivariate and multivariate logistic regression analysis was used to measure the link between appropriateness of TB treatment and treatment outcome. Odds ratios and their 95% confidence intervals were calculated. All the variables significant at $p<0.05$ in the bivariate analysis were included in the adjusted model.

Permission to carry out the study was obtained from the National Center for Tuberculosis and Lung Diseases (NCTLD) in Georgia. Local ethics approval was obtained from the Ethics Review Board of the NCTLD.

Results and discussion. The data of 13994 TB patients initially registered as DS-TB cases from 2015 and 2020 cohorts were extracted from the National Tuberculosis Electronic Register. According to the inclusion criteria, 8468 TB patients with known DST results and treatment outcomes were selected as the study participants (Fig. 1). From this, at initial stage of TB diagnosis based on rapid molecular gDST results the appropriate treatment regimen was prescribed and later, within period of 8 weeks treatment, based on pDST results the appropriateness of this regimen was confirmed in 8284 (97.8%) cases. These patients were defined as the group, for whom in period between gDST and pDST results an appropriate treatment regimen was used. In 184 (2.2%) cases, based on pDST, resistance to the different first and second line anti-TB drugs and therefore non-appropriateness of initially prescribed 2 months treatment was identified. These patients were defined as the group for whom before pDST results an inappropriate treatment regimen was used.

As the first stage the socio-demographic and clinical characteristics of selected 8468 (100%) TB patients were summarized (Table 1). From the total 8468 (100%) patients, who initially were registered as the DS-TB cases, finally based on gDST and pDST results, the DS-TB was confirmed in 7451 (88%) cases; In 730 (8.6%) cases mono- and poly-resistance and in 287 (3.4%) cases Rifampicin, Multi- or Extensively drug resistant Tuberculosis (RR/MDR/XDR-TB) was detected.

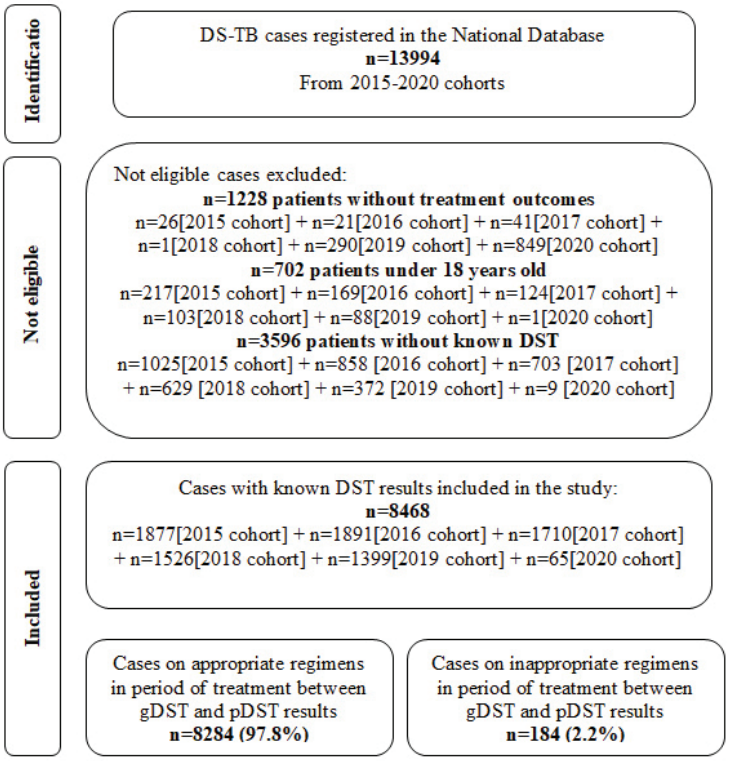


Fig. 1. Study flow chart

Table 1. Socio-demographic and clinical characteristics of the study participants, N=8468 (TB patients, initially diagnosed as DS-TB cases; Georgia; 2015–2020 cohorts)

Categories	Subcategories	Total N=8468
Gender (n,%)	Female	2220 (26.2%)
	Male	6248 (73.8%)
Age (n,%)	18-34	2662 (31.4%)
	35-54	3450 (40.7%)
	55	2356 (27.8%)
Region (n,%)	High	2622 (31%)
	Low	1633 (19.3%)
	Middle	4213 (49.8%)

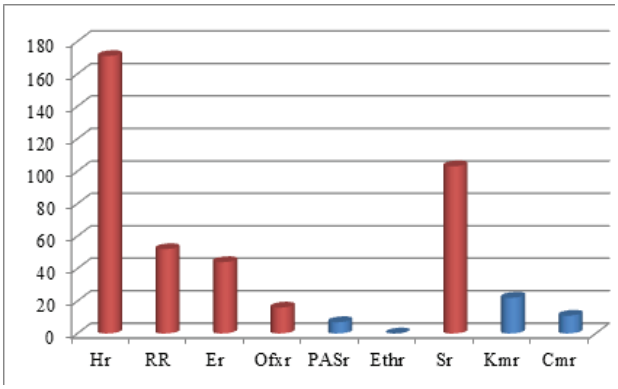
Categories	Subcategories	Total N=8468
Employment (n,%)	Employed	1057 (12.5%)
	Military	17 (0.2%)
	Minor	84 (1%)
	Unemployed	7040 (83.1%)
	Unknown	270 (3.2%)
HIV(+) (n,%)	No	6973 (82.3%)
	Unknown	1328 (15.7%)
	Yes	167 (2%)
HCV(+) (n,%)	No	1019 (12%)
	Unknown	7265 (85.8%)
	Yes	184 (2.2%)
TB Form (n,%)	EPTB	404 (4.8%)
	PTB	8064 (95.2%)
TB Case (n,%)	New Case	6552 (77.4%)
	Previously Treated Case	1916 (22.6%)
AFB(+) at diagnosis (n,%)	No	4057 (47.9%)
	Not Done	480 (5.7%)
	Yes	3931 (46.4%)
Xpert/MTB(+) (n,%)	No	400 (4.7%)
	No Result	78 (0.9%)
	Unknown	769 (9.1%)
	Yes	7221 (85.3%)
Xpert/RR(+) (n,%)	Indeterminate	102 (1.2%)
	No	6874 (81.2%)
	Unknown	1283 (15.2%)
	Yes	209 (2.5%)
Culture (+) (n,%)	No	664 (7.8%)
	Not done	37 (0.4%)
	Unknown	605 (7.1%)
	Yes	7162 (84.6%)
Bacteriological Confirmation (n,%	C+Yes	1247 (14.7%)
	Xpert/C+Yes	5915 (69.9%)
	Xpert+Yes	1306 (15.4%)
DST type (n,%)	gDST	7074 (83.5%)
	pDST	1394 (16.5%)
Hr (n,%)	No	5651 (66.7%)
	Unknown	1976 (23.3%)
	Yes	841 (9.9%)
RR (notXpert) (n,%)	No	6331 (74.8%)
	Unknown	1965 (23.2%)
	Yes	172 (2%)

Categories	Subcategories	Total N=8468
Er (n,%)	No	6115 (72.2%)
	Unknown	2160 (25.5%)
	Yes	193 (2.3%)
Sr (n,%)	No	4076 (48.1%)
	Unknown	2714 (32.1%)
	Yes	1678 (19.8%)
Kmr (n,%)	No	150 (1.8%)
	Unknown	8250 (97.4%)
	Yes	68 (0.8%)
Cmr (n,%)	No	179 (2.1%)
	Unknown	8250 (97.4%)
	Yes	39 (0.5%)
Ofxr (n,%)	No	162 (1.9%)
	Unknown	8238 (97.3%)
	Yes	68 (0.8%)
Etor (n,%)	No	21 (0.2%)
	Unknown	8445 (99.7%)
	Yes	2 (0%)
PASr (n,%)	No	139 (1.6%)
	Unknown	8307 (98.1%)
	Yes	22 (0.3%)
Resistance type (n,%)	DS-TB	7451 (88%)
	Mono/PDR-TB	730 (8.6%)
	RR/MDR/XDR-TB	287 (3.4%)
Appropriateness of Regimen (n,%)	Appropriate regimen	8284 (97.8%)
	Inappropriate regimen	184 (2.2%)
AFB(+) at II month (n,%)	No	6040 (71.3%)
	Not done	380 (4.5%)
	Unknown	1284 (15.2%)
	Yes	764 (9%)
AFB(+) at III month (n,%)	No	778 (9.2%)
	Not done	267 (3.2%)
	Unknown	7204 (85.1%)
	Yes	219 (2.6%)
AFB(+) at V month (n,%)	No	5499 (64.9%)
	Not done	878 (10.4%)
	Unknown	1941 (22.9%)
	Yes	150 (1.8%)
AFB(+) at VI month (n,%)	No	5443 (64.3%)
	Not done	794 (9.4%)
	Unknown	2131 (25.2%)

Categories	Subcategories	Total N=8468
	Yes	100 (1.2%)
Treatment Outcome (n,%)	Successful	6833 (80.7%)
	Unsuccessful	1635 (19.3%)
Treament Outcome_1 (n,%)	Completed	990 (11.7%)
	Cured	5843 (69%)
	Default	783 (9.2%)
	Died	395 (4.7%)
	Failure	268 (3.2%)
	Moved To Cat Four	39 (0.5%)
	Not Evaluated	136 (1.6%)
	Transfer Out	14 (0.2%)

HIV – human immunodeficiency virus; RR-TB – rifampicin-resistant tuberculosis; MDR-TB – multidrug-resistant tuberculosis; pre-XDR-TB – pre-extensively drug-resistant tuberculosis; XDR-TB – extensively drug-resistant tuberculosis

From 184 patients, for whom between gDST and pDST results an inappropriate 2 month treatment was used, in majority of cases the resistance to the Isoniazid was detected (171 - 93%). Rifampicin resistance was detected in 52 (28%) cases, Ethambutol resitance in 44 (24%) cases, Ofloxacin - in 16 (9%) and Streptomycin resistance in 103 (56%) cases (Fig. 2).



Hr - Isoniazid resistance; RR –Rifampicin resistance; Er – Ethambutol resistance; Ofxr – Ofloxacin resistance; PASr - Para-aminosalicylic acid resistance; Etor – Ethionamide resistance; Sr - Streptomycin resistance; Kr –Kanamycin resistance; Cmr – Capreomycin resistance

Fig. 2. Detected resistance to the first and second line anti-TB drugs in patients on inappropriate treatment regimen (N=184)

At initial stage of TB diagnosis 3931 (46.4%) patients had the AFB(+) results. The same AFB(+) results were defined at the end of the II month treatment in 764 (9%) cases, at the end of III month in 219 (2.6%) cases, at the end of V month in 150 (1.8%) cases and at the end of treatment in 100 (1.2%) cases.

In all study participants (N=8468) TB was bacteriologically confirmed and DST profile of all patients was known. In 5915 (69.9%) cases TB was confirmed based on Xpert MTB/RIF test and culture examination together. In 1306 (15.4%) cases TB was confirmed based on Xpert tests only. In 1247 (14.7%) cases TB was confirmed based on culture (+) results onl .

Based on study data discordance between Xpert MTB/RIF and culture tests were revealed. From all 7221 (85.3%) Xpert (MTB+) cases, only 5915 cases were culture positive too (in 37 cases culture was not done and in 605 cases culture results was unknown). All 400 (4.7%) patients with Xpert (MTB-) results, were Culture (+). In 664 cases with Xpert (MTB+) results, Culture was negative (Table 2).

The successful treatment outcome was defined in 6833 (80.7%) (“Cured” in 5843 (69%) and “Completed” in 990 (11.7%) cases) and unsuccessful outcome in 1635 (19.3%) cases (“Lost to follow-up” in 783 (9.2%), “Death” in 395 (4.7%), “Failure” in 268 (3.2%), “Not evaluated” in 136 (1.6%), “Moved to category four” in 39 (0.5%) and “Transfer out” in 14 (0.2%) cases).

All key factors were analyzed for association with the treatment outcomes. The adjusted analysis was used for factors defined as significantly associated with the treatment outcomes (Table 3).

Table 2. Discordance between Xpert MTB/RIF and Culture tests results

		Culture results			
Xpert MTB/RIF test results	**N=8468**	**No N=664**	**Not done N=37**	**Unknown N=605**	**Yes N=7162**
No	400 (4.7%)	0 (0%)	0 (0%)	0 (0%)	400 (5.6%)
No Result	78 (0.9%)	0 (0%)	0 (0%)	0 (0%)	78 (1.1%)
Unknown	769 (9.1%)	0 (0%)	0 (0%)	0 (0%)	769 (10.7%)
Yes	7221 (85.3%)	664 (100%)	37 (100%)	605 (100%)	5915 (82.6%)

Table 3. Factors associated with TB treatment outcomes
(TB patients, initially diagnosed as DS-TB cases; Georgia; 2015–2020 cohorts)

Categories	Subcatego-ries	Total N=8468	Successful N=6833	Unsuccess-ful N=1635	Bivariate			Multivariate		
					Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Gender (n,%)	Female	2220 (26.2%)	1925 (28.2%)	295 (18%)	**1.78**	**[1.55, 2.04]**	**<0.001**	**1.69**	**[1.47, 1.94]**	**<0.001**
	Male	6248 (73.8%)	4908 (71.8%)	1340 (82%)	1			ref.	ref.	ref.
Age (n,%)	18-34	2662 (31.4%)	2296 (33.6%)	366 (22.4%)	1	-	-			
	35-54	3450 (40.7%)	2724 (39.9%)	726 (44.4%)	0.6	[0.52, 0.69]	<0.001			
	55	2356 (27.8%)	1813 (26.5%)	543 (33.2%)	0.53	[0.46, 0.62]	<0.001			
Region (n,%)	High	2622 (31%)	2071 (30.3%)	551 (33.7%)	1	-	-	ref.	ref.	ref.
	Low	1633 (19.3%)	1358 (19.9%)	275 (16.8%)	**1.31**	**[1.12, 1.54]**	**<0.001**	0.7	[0.6, 0.83]	<0.001
	Middle	4213 (49.8%)	3404 (49.8%)	809 (49.5%)	1.12	[0.99, 1.26]	0.0681	0.84	[0.74, 0.95]	0.0059
HIV (n,%)	No	6973 (82.3%)	5812 (85.1%)	1161 (71%)	1	-	-			
	Unknown	1328 (15.7%)	915 (13.4%)	413 (25.3%)	0.44	[0.39, 0.51]	<0.001			
	Yes	167 (2%)	106 (1.6%)	61 (3.7%)	0.35	[0.25, 0.48]	<0.001			
HCV (n,%)	No	1019 (12%)	829 (12.1%)	190 (11.6%)	1	-	-			
	Unknown	7265 (85.8%)	5883 (86.1%)	1382 (84.5%)	0.98	[0.82, 1.15]	0.774			
	Yes	184 (2.2%)	121 (1.8%)	63 (3.9%)	0.44	[0.31, 0.62]	<0.001			
TB Form (n,%)	EPTB	404 (4.8%)	338 (4.9%)	66 (4%)	1.24	[0.94, 1.62]	0.121			
	PTB	8064 (95.2%)	6495 (95.1%)	1569 (96%)	1					
TB Case (n,%)	New Case	6552 (77.4%)	5498 (80.5%)	1054 (64.5%)	**2.27**	**[2.02, 2.55]**	**<0.001**	**2.15**	**[1.91, 2.42]**	**<0.001**
	Previously Treated Case	1916 (22.6%)	1335 (19.5%)	581 (35.5%)	1			ref.	ref.	ref.
DST type (n,%)	gDST	7074 (83.5%)	5685 (83.2%)	1389 (85%)	0.88	[0.76, 1.02]	0.0856			
	pDST	1394 (16.5%)	1148 (16.8%)	246 (15%)	1					
FL drugs Resistance (n,%)	No	5546 (65.5%)	4658 (68.2%)	888 (54.3%)	1	-	-			
	Unknown	1897 (22.4%)	1553 (22.7%)	344 (21%)	0.86	[0.75, 0.99]	0.0318			
	Yes	1025 (12.1%)	622 (9.1%)	403 (24.6%)	0.29	[0.25, 0.34]	<0.001			
SL drugs Resistance (n,%)	No	49 (0.6%)	24 (0.4%)	25 (1.5%)	1	-	-			
	Unknown	6724 (79.4%)	5536 (81%)	1188 (72.7%)	4.85	[2.76, 8.53]	<0.001			
	Yes	1695 (20%)	1273 (18.6%)	422 (25.8%)	3.14	[1.78, 5.56]	<0.001			

Categories	Subcategories	Total N=8468	Successful N=6833	Unsuccessful N=1635	Bivariate			Multivariate		
					Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Resistance type (n,%)	DS-TB	7451 (88%)	6212 (90.9%)	1239 (75.8%)	1	-	-			
	Mono/PDR-TB	730 (8.6%)	570 (8.3%)	160 (9.8%)	0.71	[0.59, 0.86]	<0.001			
	RR/MDR/ XDR-TB	287 (3.4%)	51 (0.7%)	236 (14.4%)	0.04	[0.03, 0.06]	<0.001			
TB Regimen (n,%)	Appropriate	8284 (97.8%)	6726 (98.4%)	1558 (95.3%)	**3.11**	**[2.31, 4.19]**	**<0.001**	**3.3**	**[2.43, 4.48]**	**<0.001**
	Inappropriate	184 (2.2%)	107 (1.6%)	77 (4.7%)	1			ref.	ref.	ref.

TB– tuberculosis; DS-TB – Drug susceptibility tuberculosis; HIV – human immunodeficiency virus; HCV- Hepatitis C virus; DST – Drug susceptibility testing; gDST – Genotypic Drug susceptibility testing; pDST – Phenotypic Drug susceptibility testing; FL – First line; SL – Second line; Mono DR-TB – Mono drug resistant tuberculosis; PDR-TB – Poly drug resistant tuberculosis; RR-TB – Rifampicin resistant tuberculosis; MDR-TB – multidrug-resistant tuberculosis; XDR-TB – extensively drug-resistant tuberculosis; ref. – reference category

In bivariate analysis, TB treatment success was positively associated with the appropriate treatment regimen (OR 3.11; 95% CI [2.31, 4.19]; p<0.001); female gender (OR 1.78; 95% CI [1.55–2.04]; p<0.001); new case (OR 2.27; 95% CI [2.02-2.55]; p<0.001); and with living in the region where TB prevalence is low (OR 1.31; 95% CI [1.12–1.54]; p<0.001).

Adjusted analysis shows significant association of a successful TB treatment outcome with the appropriate treatment regimen (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), female gender (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) and with new TB case (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

According to the study data in majority of cases (8284 (97.8%)) appropriateness of initially prescribed regimen was confirmed. This means, that the treatment regimen prescribed based on initial gDSTs results, with high reliability is in line with pDST results and in majority of cases can lead to the successful outcome.

Based on the study data, in a small but significant number of patients (184 (2.2%)) pDST revealed inappropriateness of initially prescribed regimen and this inappropriateness in majority of cases (171 (93%)) was related with using of resistant Isoniazid in 2 month period before pDST results. Isoniazid is the key anti –TB drug and in case of Isoniazid mono- or poly-resistant TB cases specific Hr-TB regimen is recommended [11]. The possibility to prescribe this regimen in timely manner should be maximized by availability of rapid, highly sensitive gDSTs for maximum number of TB patients. This finding also addresses the need for timely detection of susceptibility to the other drugs to which resistance was less frequently detected, although it was still significant (Rifampicin resistance was detected in 52 (28%) cases, Ethambutol resitance in 44 (24%) cases and Ofloxacin resistance in 16 (9%) cases).

The main finding of our study confirms our initial hypothesis. The study results show a significant association between treatment with appropriate regimen and successful outcome (OR 3.11; 95% CI [2.31, 4.19]; p<0.001). This finding emphasizes the importance of drug susceptibility test results in guiding regimen selection. Therefore, there is urgent need for expansion of laboratory capacity to perform rapid drug susceptibility tests for all potentially used TB drugs.

Adjusted analysis show, that in parallel with “Appropriate treatment”, the “Female gender” and the “New case” are significantl associated with successful TB treatment outcomes, which is in line with the results of previously conducted similar studies [12,13].

The separate discussion is needed due the discordance, which was revealed between GeneXpert and culture tests results. Unfortunately, based on the National Tuberculosis Electronic Register it’s not possible to differentiate in which case the Xpert MTB/RIF and in which the Xpert MTB/RIF Ultra was used and therefore, based on our data, we were unable to compare Culture and Xpert or Xpert Ultra tests sensitivities. Farther studies are needed to assess degree, reasons and results of discordance between genotypic and phenotypic DSTs. However, even without these studies, based on existing data we can conclude that implementation of the new tests (e.g. WGS or others, depended on the available evidences and country decision) is needed for early and accurate identification of individual, complete DST profiles and successful treatment of TB patients.

Limitations of the study. Study data includes important information about injectable agents (Cm and Km), but it was not underlined and covered in the discussion, because, in line with latest WHO guidelines (2019), Cm and Km are no longer recommended for DR-TB treatment [11]. It would be interesting to review data about Pyrazinamide (one of the first line anti-TB drug), but due the insufficien reliability of currently available Pyrazinamide susceptibility testing, these data were not included in the study.

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SUMMARY

COMPLIANCE OF INITIALLY PRESCRIBED ANTI-TUBERCULOSIS TREATMENT REGIMENS WITH COMPLETE DRUG SUSCEPTIBILITY TEST RESULTS AND ITS ASSOCIATION WITH TREATMENT OUTCOMES IN GEORGIA (2015-2020)

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Georgia has countrywide access to the genotypic and phenotypic drug susceptibility testing (gDST and pDST), however identification of susceptibility to the different anti-Tuberculosis (TB) drugs in different time period, not in all cases gives us opportunity to simultaneously know susceptibility to the all anti-TB drugs and to build an appropriate treatment regimens based on complete individual DST profile in timely manner. Initial TB treatment regimen prescribed based on gDST results not in all cases may be compliant with complete DST profile, which may be detected based on pDST results within eight weeks only. It's important to know proportion of TB patients, who in period between gDST and pDST results are treated with regimens which is non-compliant with complete individual DST profile and how the use of these inappropriate treatment regimens may affect TB treatment outcome.

The aim of the study was to assess compliance of anti-TB treatment regimens with complete DST profile in period between gDST and pDST results and its association with treatment outcomes among patients who initially was registered as drug sensitive TB (DS-TB) cases in Georgia.

A retrospective cohort study was conducted among 8468 patients initially registered as DS-TB adult (18+) cases, from 2015 - 2020 cohorts, whose DST profiles and anti-TB treatment outcomes was known.

Adjusted analysis of the study participants data [8468 (100%)] shows significant association of a successful TB treatment outcome with the "appropriate treatment regimen" (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), "female gender" (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) and with "new TB case" (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

From 184 patients, for whom between gDST and pDST results an inappropriate 2 month treatment was used, in 171 (93%) cases the resistance to the Isoniazid was detected (Rifampicin resistance in 52 (28%), Ethambutol resitance in 44 (24%) and Ofloxacin rsistance in 16 (9%) cases was detected).

Based on study data discordance between Xpert MTB/RIF and culture tests were revealed. From all 7221 (85.3%) Xpert (MTB+) cases, only 5915 cases were culture positive too. All 400 (4.7%) patients with Xpert (MTB-) results were Culture positive. In 664 cases with Xpert (MTB+) results, Culture was negative.

For successful outcomes, all efforts should be done to have the individual and complete DST profiles of all patients at initial stage of TB diagnosis. Otherwise, in case of delayed DST results anti-TB treatment for a certain period maybe inappropriate and can raise the risk of non-successful outcome.

Keywords: Tuberculosis, DS-TB, phenotypic and genotypic DST, susceptibility, resistance, compliance, treatment outcomes.

РЕЗЮМЕ

ОЦЕНКА СООТВЕТСТВИЯ РЕЖИМОВ ПРОТИВОТУБЕРКУЛЕЗНОГО ЛЕЧЕНИЯ ПОЛНОМУ ПРОФИЛЮ ТЕСТИРОВАНИЯ НА ЛЕКАРСТВЕННУЮ ЧУВСТВИТЕЛЬНОСТЬ И ЕГО СВЯЗЬ С ИСХОДАМИ ЛЕЧЕНИЯ БОЛЬНЫХ ТУБЕРКУЛЕЗОМ В ГРУЗИИ

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Генотипическое и фенотипическое тестирование на лекарственную чувствительность (ТЛЧ) проводится на всей

территории Грузии, однако выявление чувствительности к различным противоткберкулезным препаратам в разные периоды времени не во всех случаях позволяет одновременно иметь информацию о восприимчивости ко всем противотуберкулезным препаратам и своевременно строить соответствующие режимы лечения на основе полного индивидуального профиля ТЛЧ. Изначальный режим лечения туберкулеза, назначенный на основе результатов генотипического ТЛЧ, не во всех случаях может соответствовать полному профилю ТЛЧ, который на основе результатов фенотипического ТЛЧ может быть выявлен только в течение восьми недель. Важно знать долю пациентов с туберкулезом, которые в период между результатами генотипического и фенотипического ТЛЧ лечатся режимами, несоответствующими полному индивидуальному профилю ТЛЧ, и как использование этих несоответствующих режимов лечения может повлиять на результаты лечения туберкулеза.

Цель исследования - оценка соответствия режимов противотуберкулезного лечения полному профилю тестирования на лекарственную чувствительность в период между результатами генотипического и фенотипического тестирования и связь с результатами лечения пациентов, зарегистрированных как случаи лекарственно устойчивого туберкулеза в Грузии.

Ретроспективное когортное исследование проведено среди 8468 пациентов, первоначально зарегистрированных как взрослые (+18 лет) случаи лекарственно чувствительного туберкулеза с 2015 по 2020 гг., чьи профили ТЛЧ и исходы противотуберкулезного лечения были известны.

Анализ данных участников исследования показывает статистический значимую связь успешного исхода лечения туберкулеза с «соответствующим режимом лечения» (уточненное ОШ 3,3, 95% ДИ: (2,43-4,48), p<0,001), “женским полом” (уточненное ОШ 1,69, 95% ДИ: 1,47 - 1,94, p < 0,001) и с “новым случаем туберкулеза” (уточненное ОШ 2,15, 95% ДИ: 1,91-2,42, p<0,001).

Из 184 пациентов, для которых между результатами генотипического и фенотипического ТЛЧ использовано несоответствующее двухмесячное лечение, в 171 (93%) случае выявлена устойчивость к изониазиду, устойчивость к рифампицину - в 52 (28%), к этамбутолу - в 44 (24%) и к офлоксацину - в 16 (9%) случаях.

На основании данных исследования выявлено несоответствие между результатами Xpert MTB/RIF и культурального исследования. Из всех Xpert (MTB+) 7221 (85,3%) случая только в 5915 случаях выявлен культура-положительный результат. Все 400 (4,7%) пациентов с Xpert (MTB-) результатами были положительными по культуре. В 664 Xpert (MTB+) случаях результат культурального исследования был отрицательным.

Для успешного лечения туберкулеза необходимо на начальной стадии диагностики получить индивидуальные и полные профили ТЛЧ пациентов. В случае задержки результатов ТЛЧ противотуберкулезное лечение в течение определенного периода может быть несоответствующим и увеличить риск безуспешного лечения.

რეზიუმე

საწყისად დანიშნული ტუბსაწინააღმდეგო რეჟიმის შესაბამისობა მედიკამენტებისადმი მგრძნობელობის ტესტირების შედეგებთან და მისი ასოცირება მკურნალობის გამოსავალთან

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ტუბერკულოზისა და ფილტვის დაავადებათა ეროვნული ცენტრი, თბილისი, საქართველო

საქართველოში ქვეყნის მასშტაბით ხელმისაწვდომია მედიკამენტებისადმი მგრძნობელობის გენოტიპური და ფენოტიპური ტესტირება (gDST და pDST), თუმცა სხვადასხვა ტუბსაწინააღმდეგო მედიკამენტის მიმართ მგრძნობელობის სხვადასხვა დროს განსაზღვრა ყველა პაციენტთან მედიკამენტებისადმი მგრძნობელობის ერთდროულად განსაზღვრისა და სრულ, ინდივიდუალურ DST პროფილთან შესაბამის ადექვატური სამკურნალო რეჟიმის დროულად დანიშვნის შესაძლებლობას არ იძლევა. gDST-ის შედეგზე დაყრდნობით შერჩეული საწყისი ტუბსაწინააღმდეგო სამკურნალო რეჟიმი ყველა შემთხვევაში შეიძლება არ იყოს შესაბამისი იმ სრულ DST პროფილთან, რომელიც მხოლოდ pDST-ით 8 კვირის ვადაში ხდება ცნობილი. მნიშვნელოვანია განისაზღვროს იმ პაციენტთა წილი, რომლებიც gDST და pDST შედეგებს შორის პერიოდში სრულ, ინდივიდუალურ DST პროფილთან შეუსაბამო მკურნალობას ღებულობს და შეფასდეს არაადექვატური რეჟიმის გამოყენება მკურნალობის გამოსავალზე

კვლევის მიზანი - საქართველოში საწყისად სენსიტიური ტუბერკულოზის მქონე პაციენტებად დარეგისტრირებულ შემთხვევებთან, მედიკამენტებისადმი მგრძნობელობის გენოტიპური და ფენოტიპური ტესტირების შედეგების პერიოდში, ტუბსაწინააღმდეგო სამკურნალო რეჟიმის სრულ DST პროფილთან შესაბამისობის და ამ შესაბამისობის მკურნალობის გამოსავალთან ასოცირების შესწავლა.

რეტროსპექტული კოჰორტული კვლევა 2015-2020 წლების კოჰორტის, +18 ასაკობრივი ჯგუფის, საწყისად სენსიტიური ტუბერკულოზით დარეგისტრირებულ ისეთ 8468 პაციენტთან ჩატარდა, რომლების DST პროფილი და ტუბსაწინააღმდეგო მკურნალობის გამოსავალი ცნობილი იყო. კვლევის მონაწილეთა მონაცემების დაზუსტებულმა ანალიზმა აჩვენა, რომ ტუბსაწინაარმდეგო მკურნალობის წარმატებული გამოსავალი სარწმუნოდ ასოცირდება ადექვატური სამკურნალო რეჟიმით მკურნალობასთან (adjusted OR 3.3, 95% CI: (2.43–4.48), p<0.001), მდედრობით სქესთან (adjusted OR 1.69, 95% CI: 1.47 – 1.94, p<0.001) და „ახალ“ შემთხვევასთან (adjusted OR 2.15, 95% CI: 1.91–2.42, p<0.001).

184 პაციენტთაგან, რომლებსაც gDST და pDST შედეგებს შორის 2-თვიან პერიოდში არაადექვატური ტუბსაწინააღმდეგო რეჟიმი იყო დანიშნული, 171 (93%)-ს იზონიაზიდისადმი რეზისტენტობა გამოუვლინდა, რიფამპიცინისადმი რეზისტენტობა - 52 (28%)-ს, ეტამბუტოლისადმი - 44 (24%)-ს, ოფლოქსაცინისადმი - 16 (9%) პაციენტს.

კვლევის ფარგლებში გამოვლინდა შეუსაბამობა Xpert MTB/RIF და კულტურალური კვლევის შედეგებს შორის. ჯამში, სულ Xpert (MTB+) შედეგის მქონე 7221 (85.3%) პაციენტისგან, კულტურა-დადებითი შედეგი 5915 პაციენტთან დაფიქსირდა. Xpert (MTB-) შედეგის მქონე ყველა 400 (4.7%) პაციენტი აღმოჩნდა კულტურა-დადებითი. 664 Xpert (MTB+) შედეგის მქონე პაციენტთი იყო კულტურა-უარყოფითი.

დადებითი ტუბსაწინააღმდეგო მკურნალობის გამოსავალის მისაღწევად აუცილებელია ტუბერკულოზის საწყისი დიაგნოსტიკისთანავე ყველა პაციენტის სრული, ინდივიდუალური DST პროფილის გამოვლენა. მედიკამენტებისადმი მგრძნობელობის ტესტის გვიანი შედეგების პირობებში დანიშნული ტუბსაწინააღმდეგო რეჟიმი გარკვეული პერიოდის მანძილზე შესაძლოა არაადექვატური იყოს და გამოიწვიოს მკურნალობის წარუმატებელი გამოსავლის რისკის მატება.

DIAGNOSTICS AND TREATMENT OF GENITAL INVASION CAUSED BY TRICHOMONAS VAGINALIS AND POSSIBLY OTHER RELATED SPECIES (PENTATRICHOMONAS HOMINIS AND TRICHOMONAS TENAX) IN PATIENTS WITH IMMUNODEFICIENCY

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Trichomoniasis disease despite its intensive study is nowadays a considerable clinical problem in practice of dermatovenereologists, urologists and gynecologists. Trichomonas invasion has a negative influence on patient fertility and quality of life [11]. According to data of the World Health Organization in recent decades global incidence rate in urinary trichomoniasis (ICD-10, A59) is about 270 million people per year [17].

Until recently it has been believed that only *Trichomonas vaginalis* can exist in human genitourinary tract [18]. However, inclination of Protozoa to evolutionary changes and significant shift in patterns of sexual behaviour, in particular, frequent anal and oral sex practice resulted in the existence of other species of trichomonads in human genitourinary tract, namely, *Pentatrichomonas hominis* and *Trichomonas tenax* [12,13,18].

In Ukraine investigations on determination of *Pentatrichomonas hominis* and *Trichomonas tenax* in the genitourinary tract of patients with sexually transmitted infections (STI) were conducted for the first time in 2013-2017. The mentioned microorganisms were found in more than a third of patients with advanced progressive illness [9,13,19]. In the investigation the abstinence not less than 2 days was strictly observed that made it impossible to consider *Pentatrichomonas hominis* and *Trichomonas tenax* as a transitory microflora. Duration of the investigation minimized the probability of outer contamination. Persistence of chronic inflammatio in the patients allowed us to suppose a certain ethiological role of *Pentatrichomonas hominis* and *Trichomonas tenax* in it. Moreover, detection of trichomonad species in genitourinary tract, their elimination, and certain behavioural modifications may play a decisive role in prevention of trichomonias recurrences or re-infections [20]. Besides, it should be also noted that phagocytic features are peculiar to all *Protozoa*, in particular, trichomonads. By phagocytosis carried out by any *Protozoa*, a part of microorganisms is not destroyed completely – they are preserved unhurt (incomplete phagocytosis) inside the cytozoon [3]. In case of incomplete phagocytosis of cocci, diplococci, mycoplasma, Chlamydia, bacillary forms, viruses passing out by death of trichomonads are able to support inflammatory process in urogenital tracts that is often considered to be "untreatable" trichomoniasis or "posttrichomonal" lesions [11]. That's why Protozoa, whereof direct pathogenicity on human urinary system has not been finally proved. First of all, we should consider *Trichomonas tenax* and *Pentatrichomonas hominis,* at least as disease-producing agents of STI. For this reason, eradication of *Trichomonas tenax* and *Pentatrichomonas hominis* from human urinary system should be required.

Thus, urgency of the issue of urinary trichomoniasis is connected with a high incidence of disease as well as possibility of colonization of the urinary system with "new" agents as a result of partial change of their biological properties [9,12,13]. Consideration of presence of the agents, which are morphologically similar to *Trichomonas vaginalis*, but different from them by taxonomic belonging, will present an opportunity of more accurate diagnostics of trichomoniasis and its more successful treatment and prevention.

As it is known from the literature, infectious affections of the urinary system often become chronically persistent or resistant to many treatments in the case of immunodeficiency [16]. Immunodeficienc (ICD-10, D80 – D89) may be determined as impairment of structure and function of any chain of the immune system, body's loss of ability to present resistance to any infections and recover impairments of its organs. Besides, the process of body rejuvenation slows down or stops at all by immunodeficiency [2]

Based on the above mentioned, we can come to the conclusion that it is necessary to develop a new effective treatment method for STI, in particular, trichomoniasis on the background of immunological disorders [15].

Nowadays, therapeutic methods including prescription of α and ß- defensin-containing drugs for the purpose of immunocorrection are one of the most promising. PROPES® drug developed by the Research and Development enterprise "NIP" (Ukraine) at the present time is the only registered in our country immu-

nomodulatory drug that contains defensins. It is extracted from embryonic tissue of cattle as the result of peculiar proteolysis. Defensins are peptides with anti-infective and anti-cancer activity: α-defensins are characterized by predominantly antibacterial and antiviral properties; ß- defensins, moreover, are also active in relation to pathogenic fungi as well as able to display significant anti-tumor activity [10]. PROPE ® stimulates functional activity of mononuclear phagocytes and natural killer cells, in other words, activates inandate immunity of the body. It inhibits production of anti-inflammatory cytokines by allergic diseases. The drug has significant antitoxic effects, improves hepatic functions, inhibits development of neoplastic processes, contributes to tumour regression by its resorption. It doesn't have mutagenic, embryotoxic, teratogenic, pyrogenic and hemolytic properties. One of the most significant advantages of PROPES® is its nontoxicity ensuring great therapeutic width of the drug [4]. In medical practice PROPES® is recommended to treat various diseases on the background of disorders of immunological reactivity. The ability to recover active and satisfactory work of the immune system, regulation of balance between different chains of anti-infectious protection, opens for the drug opportunities to improve functioning of human body under the conditions of immunodeficienc . It has been established that under its influence quantity of T- lymphocytes increases, ratio of their subpopulations and level of serum factor of α-tumour necrosis is normalized and level of interleukin-4 reaches the level of healthy people [6].

Taking into consideration the above mentioned, it may be concluded that there is a great need to develop a new effective treatment method for chronic trichomoniasis on the background of immunodeficienc , in particular, using drugs belonging to the group of defensins (PROPES®). of species belonging of trichomonads, herewith, may facilitate the effective taking clinical diagnostic, and therapeutic measures.

Objective - studying species belonging of the agents of chronic trichomoniasis of the urinary system in patients with sexually transmitted infections and immunodeficienc , efficienc of their treatment.

Material and methods. Certain study group was selected among 77 persons, patients with sexually transmitted infections of both genders (29 males and 48 females), which sought specialized medical care in relation to inflammation of the genitourinary system on the background of immunodeficienc . Final composition of the study group, consisting of 32 (41.6%) patients, was formed according to the results of Protozoan invasion of the urogenital system detected in each member. Thus, each study group had 22 (68.8%) females and 10 males (31.2%) aged 20 to 48 years old. Mean age was 32±2.5. All patients, which were under care, had advanced progress of affection of the genitourinary system. Sense of discomfort in the genitourinary organs and discharges prevailed among patients' complaints.

To study condition of the immune system, determination of absolute lymphocyte count in blood serum, levels of T- lymphocytes (CD3+), T helper cells (CD4+), cytotoxic T-lymphocytes (CD8+); immunoregulatory index Th/Tc; levels of active T-lymphocytes, B-lymphocytes (CD22+), killer lymphocytes (CD18+), T helper cells, 0-lymphocytes; lymphocyte blastogenic response with PHA, phagocytic index, phagocytic coefficient NBT test as well as Igg A,G,M levels was used.

In order to detect agents of trichomonas invasion, the method of real-time polymerase chain reaction, DT-96 amplifie , primers for detection of *Trichomonas vaginalis* (produced by R&D company DNA-technology, Russian Federation) and original uniquely designed primers for detection of *Trichomonas tenax* and *Pentatrichomonas hominis* was applied [14].

For the purpose of immunocorrection, the drug PROPES® was introduced to the patients under study intramuscularly according to the treatment pattern for diseases connected with disorders of immunological status, namely, 2 ml each alternate day within 20 days [6]. Its administration began simultaneously with the course of specific therapy of trichomonas invasion [7], in particular, ornidazol was prescribed orally 1.5 per day. The drug was taken 0.5 three times per day after meals for 10 days. On the first day of treatment daily dose of ornidazol was taken at a time during dinner. The next 10 days (from 11 to 20 days of treatment) the patients received 400 mg of Nifuratelum three times a day, regardless of meals. If necessary, in 5 days after the beginning of specific anti-protozoarian therapy, additional antimicrobial drugs were prescribed personally at the same time for the patients in order to eliminate other STI agents from the urogenital system, which are not sensitive to Nifuratelum and ornidazol.

Besides, males, if required, had finger massage of prostate and took rectal anti-inflammatory suppositories. Females had daily vaginal syringing and took vaginal tablets with Nifuratelum and Nystatin as well as suppositories with chlorohexidine consistently for 8 and 10 days, respectively. During the treatment, the patients were strictly forbidden to have sexual contacts, and in the testing period sex without barrier contraceptives was not allowed in order to prevent reinfection.

Results and discussion. *Trichomonas tenax* was detected in 12 (37.5%) of 32 patients of the study group, which had trichomonal invasion, *Pentatrichomonas hominis* – in 18 (56.3%), *Trichomonas vaginalis* – in 2 (6.2%). With regard to 77 examined patients with STI and simultaneously with immunodeficienc , *Trichomonas tenax* was found in (15.5%), *Pentatrichomonas hominis* – in 22.0%, *Trichomonas vaginalis* – in 4.1%.

As Table shows, the following overall average immunogram – quantity values significantly changed in the patients under study: (absolute) lymphocyte (count), cytotoxic T-lymphocytes (CD8+), 0-lymphocytes, active T-lymphocytes as well as immunoregulatory index Th/Tc. Moreover, value of absolute lymphocyte count was increased, probably, because of general processes of adaptation in the bodies of these patients. Value of 0-lymphocytes number was increased and active T-lymphocytes reduced, respectively. Value of cytotoxic T-lymphocytes (CD8+) was also reduced, by means of which overall average of immunoregulatory index (Th/Ts) increased significantl . Values of humoral immune chain, phagocytic index, phagocytic coefficien and NBT test remained unchanged.

Immunogram values of the patients under study were determined in 2-3 months upon their completing the course of PROPES®. As the Table shows, after treatment with PROPES®, overall mean values of immunograms recovered to normal rates. Emergence on indurations in the area of buttock during the conducted therapy was registered in 5 of 32 patients (15.6%). More 6 (18.8%) had complaints on some painfulness in the areas of PROPES® injections. Severity of the above mentioned side effects was insignificant and didn't require to stop administration of this drug or to prescribe additional pharmacological therapy for their removal. Consequently, it may be concluded that patients tolerate the drug PROPES® well or satisfactorily.

Table. Immunogram values of the patients under study with trichomonal invasion before and after administration of the drug PROPES® (n=32)

Immunogram value	Result before treatment	Result after treatment	Normal range
Absolute lymphocyte count	*3.00±0.45 x^{10}	2.3±0.42 x^{10}	1.5 – 2.4 x^{10}
T- lymphocytes (CD3+)	45±5.1%	45±5.3%	40 – 67%
T helper cells (CD4+)	33±4.4%	33±4.7%	23 – 48%
Cytotoxic T-lymphocytes (CD8+)	*12±1.7%	**18±1.6%	17 – 25%
Immunoregulatory index Th/Ts	*2.7±0.81	2.0±0.75	1.1 – 2.2
Active T- lymphocytes	*13.1±3.1%	**23±2.2%	22 – 39%
B-lymphocytes (CD22+)	30.2±6.0%	30±6.1%	15 – 35%
Killer lymphocytes (CD18+)	17.3±3.6%	17±3.5%	15 – 20%
0- lymphocytes	*25.2±4.3%	**18±1.9%	15 – 20%
Lymphocyte blastogenic response with PHA	78.4±10.1%	78±10%	70 – 82%
IgG. g/l	12.3±1.9 g/l	13.2±1.8 g/l	7.5 – 15.45
IgA. g/l	2.1±0.2 g/l	2.1±0.3 g/l	1.75 – 2.5
IgM. g/l	0.9±0.2 g/l	0.9±0.2 g/l	0.65 – 1.65
Phagocytic index	64±11%	60±11 %	40 – 80%
Phagocytic coefficie	5.2±0.7	5.8±0.4	4 – 8
NBT test	17.2±3.2	17±1.8	10 – 30

*note: * - reliability of differences between indicators of the study group and the control group of healthy persons (p<0.05);*
*** - reliability of differences between indicators of the study group and the data before treatment (p<0.05);*
n – number of examined persons

Consequently, PROPES® is highly-efficien immunocorrecting drug, which normalizes immunogram values in the corresponding patients and its usage is reasonable in the combined therapy of chronic protozoan invasions caused by various species of trichomonads on the background of immunodeficienc .

The results of the therapy in relation to elimination of pathogenic microorganisms from the urogenital system were determined according to the recommendations of the World Health Organization – in 1, 2 and 3 months upon completion of specific therapy [5]. It was possible to achieve a complete elimination of the agents of trichomonas invasion with advanced process from the urogenital system of the patients of testing group in 31 (96.9%) of 32 persons under study. They stopped to complain of discharge and discomfort. Clinical and ethological recovery came. Unsuccessful treatment of one patient (absence of elimination of *Pentatrichomonas hominis)* – can be explained by possibility of her reinfection by means of failure to observe sexual abstinence in the testing period.

Thus, the therapy was conducted with consecutive internal use of two anti-protozoarian drugs, which contain, ornidazol and nifurotel, respectively, for 10 days each. Combination of anti-protozoarian drugs of various drugs greatly improves efficienc of the corresponding treatment due to reduction of resistance on the part of pathogenic agent. Besides, application of nifurotel gives some additional advantages, first of all, connected with elimination of background microflora [8]. Duration of etiological treatment of chronic trichomonal inflammation was 20 days that corresponds to the terms of antibacterial therapy provided that internal genital organs are affe ted [1]. But in this case increased treatment duration was additionally caused also by immunodeficienc .

Different dyspeptic events occurred in the majority of patients (about 70%) of study group that is natural by enteral prescribing of the drugs belonging to nitroimidazoles. There was no need to stop the treatment started according to the suggested schedule or additional treatment directed at elimination of the side effects. It gives us the right to consider suggested method of eradication of protozoal invasion to have satisfactory tolerance for patients.

Thus, the suggested unique treatment method is effective, has satisfactory tolerance and may be recommended for empiric treatment of the urogenital system lesions associated with protozoal invasions, which are caused by *Trichomonas vaginalis, Trichomonas tenax* and *Pentatrichomonas hominis.*

Conclusions.

Trichomoniasis of the urogenital system may be nowadays caused by various species of trichomonads, namely *Trichomonas vaginalis, Trichomonas tenax* and *Pentatrichomonas hominis*.

Urinary trichomoniasis is widespread in patients with sexually transmitted infections and, simultaneously, immunodeficiency (41.6%). Moreover, *Trichomonas tenax* was revealed in 15.5%, *Pentatrichomonas hominis* – in 22%, *Trichomonas vaginalis* – in 4.1% of 77 corresponding patients.

The suggested method with consecutive application of ornidazol and nifurotel allow conducting effective treatment of chronic trichomoniasis of the urogenital system caused by its various agents. Clinical and bacteriological recovery occurred in 96.9% cases.

PROPES® is highly-efficien immunocorrecting drug, which contributes to normalization of immunogram values in the patients with immunodeficienc .

The suggested cure method of chronic trichomoniasis providing for consecutive application of anti-protist substances ornida-

zol and nifurotel on the backgrounds of the drug PROPES® (as a immunocorrecting preparation) has high efficienc and good tolerance and may be recommended for a wide clinical application.

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SUMMARY

DIAGNOSTICS AND TREATMENT OF GENITAL INVASION CAUSED BY TRICHOMONAS VAGINALIS AND POSSIBLY OTHER RELATED SPECIES (PENTATRICHOMONAS HOMINIS AND TRICHOMONAS TENAX) IN PATIENTS WITH IMMUNODEFICIENCY

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Objective - studying species belonging to the causative agents of trichomoniasis of the genitourinary system in patients with sexually transmitted infections and immunodeficienc , assessing efficiency of their treatmen

77 patients with sexually transmitted infections and immunodeficiency were examined using the method of polymerase chain reaction in order to detect trichomonas species. 32 patients were given treatment and immune system indicators dynamics were determined.

Trichomonas tenax was detected in 15.5%, *Pentatrichomonas hominis* – in 22%, *Trichomonas vaginalis* – in 4.1% of 77 examined patients. The method of combine treatment, providing for consecutive application of anti-protist substances of ornidazole and nifurotel with PROPES® taking smiltaniosly was effective to manage chronic trichomoniasis in 96.9% cases. Normalization of immune system took place.

Trichomonias is a widespread disease in patients with sexually transmitted infections and immunodeficiency at the same time (41.6%). Application of the suggested original method allows us to achieve effective cure of chronic genital trichomoniasis caused by its various trichomonas species. Administration of PROPES® could be recommended as combined treatment of trichomoniasis on the background of immunodeficienc .

Keywords: *Trichomonas vaginalis, Trichomonas tenax, Pentatrichomonas hominis,* immunodeficienc , treatment, PROPES®.

РЕЗЮМЕ

ДИАГНОСТИКА ХРОНИЧЕСКОГО ТРИХОМОНИАЗА С УЧЕТОМ ВИДОВОЙ ПРИНАДЛЕЖНОСТИ ВОЗБУДИТЕЛЕЙ И ЕГО ЛЕЧЕНИЕ У БОЛЬНЫХ С ИММУНОДЕФИЦИТОМ

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Цель исследования - определение видовой принадлежности возбудителей хронического трихомониаза мочеполовой системы у больных инфекциями, передающимися половым путем, и с иммунодефицитом и эффективности их лечения.

С целью выявления трихомонад различных видов методом полимеразной цепной реакции проведено обследование 77 пациентов (29 мужчин и 48 женщин) с инфекциями, передающимися половым путем, и с иммунодефицитом. 32 пациентам (22 женщины и 10 мужчин, средний возраст - 32±2,5 г.) с трихомониазом и иммунодефицитом проводилось лечение по оригинальной методике.

Trichomonas tenax выявлен у 12 (15,5%), Pentatrichomonas hominis – у 17 (22%), Trichomonas vaginalis - у 3 (4,1%) из 77 обследованных пациентов. Предложенный комплексный метод лечения хронического трихомониаза, предусматривающий последовательное применение протистоцидных веществ орнидазола и нифуротеля на фоне препарата пропес, оказался эффективным в 96,9% случаев. Отмечалась нормализация показателей иммунограмм.

Таким образом, следует заключить, что использование предложенного метода позволило проводить эффективное лечение хронического трихомониаза мочеполовой системы, вызванного его различными возбудителями. Применение препарата Пропес является целесообразным в комплексном лечении пациентов с трихомониазом на фоне иммунодефицита.

რეზიუმე

ქრონიკული ტრიქომონიაზის დიაგნოსტიკა გამომწვევების სახეობრივი კუთვნილების გათვალისწინებით და მისი მკურნალობა იმუნოდეფიციტით დაავადებულ ავადმყოფებში

პ. ფედორიჩი

უკრაინის სამხედრო-სამედიცინო აკადემია, კიევი, უკრაინა

კვლევის მიზანი წარმოადგენდა სქესობრივი გზით გადამდებ ინფექციურ დაავადებებით და იმუნოდეფიციტით ავადმყოფებში შარდსასქესო გზების ქრონიკული ტრიქომონიაზის გამომწვევების სახეობრივი კუთვნილების და მათი მკურნალობის ეფექტიურობის შესწავლა.

პოლიმერაზული ჯაჭვური რეაქციის მეთოდით სხვადასხვა სახეობის ტრიქომონადების გამოვლენის მიზნით ჩატარებულია სქესობრივი გზით გადამდებ ინფექციურ დაავადებებით და იმუნოდეფიციტით დაავადებული 77 (29 მამაკაცი და 48 ქალი) პაციენტის გამოკვლევა. 32 (22 ქალი და 10 მამაკაცი, საშუალო ასაკი 32±2,5 წ.) ტრიქომონიაზით და იმუნოდეფიციტით დაავადებულ პაციენტს ჩაუტარდა მკურნალობა ორიგინალური მეთოდიკით.

77 გამოკვლეულ პაციენტებში Trichomonas tenax გამოვლინდა 12 (15,5%), Pentatrichomonas hominis – 17 (22%), Trichomonas vaginalis – 3 (4,1%). ქრონიკული ტრიქომონიაზის მკურნალობის ახალი ორიგინალური კომპლექსური მეთოდი, რომელიც ითვალისწინებს პროტისტოციდული ნივთიერებების ორნიდაზოლის და ნიფურატელის თანმიმდევრულ გამოყენებას პრეპარატი პროპესის ფონზე, ეფექტიური აღმოჩნდა 96,9% შემთხვევაში, აღინიშნებოდა იმუნოგრამის მაჩვენებლების ნორმალიზება.

სქესობრივი გზით გადამდებ ინფექციურ დაავადებებით და იმუნოდეფიციტით დაავადებული ავადმყოფებში ტრიქომონიაზი გამოვლინდა 41,6% შემთხვევაში. შეთავაზებული მეთოდის გამოყენება შარდსასქესო გზების ქრონიკული ტრიქომონიაზის სხვადასხვა გამომწვევების მიერ დაავადებული პაციენტების ეფექტური მკურნალობის საშუალებას იძლევა. პრეპარატი პროპესის გამოყენება არის მიზანშეწონილი იმუნოდეფიციტის ფონზე ტრიქომონიაზით დაავადებული პაციენტების კომპლექსურ მკურნალობაში.

КЛИНИКО-МОРФОЛОГИЧЕСКИЕ И МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ ПЕРВИЧНОГО МИЕЛОФИБРОЗА И ФАКТОРЫ ПРОГНОЗА. ОПИСАНИЕ СЛУЧАЯ ТРАНСФОРМАЦИИ ПЕРВИЧНОГО МИЕЛОФИБРОЗА В ОСТРЫЙ МИЕЛОБЛАСТНЫЙ ЛЕЙКОЗ

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Первичный миелофиброз (ПМФ, хронический идиопатический миелофиброз с миелоидной метаплазией, агногенная миелоидная метаплазия, сублейкемический миелоз) в соответствии с классификацией ВОЗ (2016) относится к Ph-негативным миелопролиферативным заболеваниям [1,2,4-6,7,8,44,47].

Миелопролиферативные заболевания (МПЗ) - клональные опухоли, которые возникают на уровне стволовой кроветворной клетки и характеризуются пролиферацией одной или более клеточных линий миелопоэза в костном мозге с признаками сохранной терминальной дифференцировки. Хотя этиология МПЗ по сей день не выяснена, основной гипотезой патогенеза признана многоэтапность генетических перестроек, при которых предрасположенность к болезни реализуется под воздействием внешних факторов, повреждающих геном нормальной гемопоэтической клетки и приводящих к её злокачественной трансформации [1,2].

Помимо ПМФ, к МПЗ относят также истинную полицитемию (ИП), эссенциальную тромбоцитемию (ЭТ) и неклассифицируемые МПЗ, которые встречаются более чем у 98% пациентов.

В последние годы в расшифровке молекулярно-генетических механизмов Ph-негативных МПЗ достигнуты значительные успехи. Так, открытие мутации JAK2 V617F в 2005 г. способствовало пересмотру диагностических критериев МПЗ. Мутация JAK2 выявляется в 96% случаев при ИП, в 55% - при ЭТ и в 45-68% при ПМФ [9,11,26-28,34,35,54]. Высокая аллельная нагрузка JAK2 V617F ассоциирована с пожилым возрастом, повышенным уровнем гемоглобина, лейкоцитозом и тромбоцитопенией [12].

Патогенез ПМФ сложен и состоит из цепи событий, первичным из которых является появление патологического клона [34]. У большинства (90%) больных ПМФ встречается точечная мутация в гене янускиназы (JAK) – перестройка JAK2 V617F рецептора эритропоэтина или в генах CALR и MPL (так называемые «водительские» мутации) [42,43,45,48,56]. Кроме мутаций JAK2 выявляются соматические мутации и в других генах (VPL, TET2, ASXL, CBL, LDH1/LDH2, LNK, EZH2, LKZFL/LKaros) – «пассажирские», однако они не являются специфичными и имеют вторичный генез в цепи генетических событий [9,52]. Следует отметить, что у пациентов с одной соматической мутацией JAK2, CALR или MPL прогноз более благоприятный, чем при наличии мутаций генов TP53 и TET2. Так, мутация MPL ассоциирована с пожилым возрастом, женским полом, низким содержанием гемоглобина и числа тромбоцитов [44,47]. Мутации гена CALR имеют более благоприятный прогноз в сравнении с теми больными ПМФ, кто имеет мутации JAK2 V617F или MPL W515K/L. Кроме того, мутации в любом из генов ASXL1, EZH2, LDH1/LDH2 и SRF2 при ПМФ определены как категория высокого молекулярного риска, предсказывающая худшую общую выживаемость (ОВ) больных [15,56]. Ключевым молекулярно-генетическим механизмом в возникновении болезни могут быть активация JAK2-киназы и мутации в генах CALR или MPL, что приводит к стимуляции клеточной пролиферации [9,21,28]. Известно, что лейкемические моноциты и мегакариоциты активно продуцируют множество цитокинов (TGF-beta, FGF, VEGF), избыток которых стимулирует фиброз, неоангиогенез и приводит к остеосклерозу. Наряду с этим нарушается связь стволовых клеток с микроокружением, что способствует появлению экстрамедуллярных очагов гемопоэза, прежде всего, в селезенке и печени. Массивный выброс цитокинов – одна из причин возникновения симптомов опухолевой интоксикации и миелофиброза.

Клиническая картина ПМФ тесно связана с его патогенезом и характеризуется многообразием проявлений. Начальный период болезни у большинства пациентов может протекать бессимптомно на протяжении ряда лет. Чаще всего признаки заболевания обнаруживают случайно при исследовании периферической крови на профилактическом осмотре или по поводу сопутствующей патологии. На начальном этапе развития болезни происходит постепенное увеличение опухолевой массы. На протяжении первых лет заболевания основным проявлением является повышение риска развития тромбозов и тромбоэмболий на фоне существующей сердечно-сосудистой патологии и атеросклероза.

При длительном течении заболевания и развитии миелофиброза и остеосклероза могут появляться симптомы опухолевой пролиферации и интоксикации, ассоциированные с секрецией цитокинов, выход миелоидных предшественников в периферическую кровь с появлением экстрамедуллярных очагов кроветворения в печени и селезенке, развитие кахексии [3,43,46,52].

Длительная пролиферация опухолевого клона приводит к приобретению дополнительных мутаций и более высокой степени малигнизации. Данный процесс завершается бластной трансформацией с развитием терминальной стадии заболевания - бластной фазы (БФ), которая наблюдается у 1-2,5% больных в течение первых 10 лет ПМФ и у 5-8% - при большей длительности заболевания [52,56].

Выделяют две фазы ПМФ, отражающие степень прогрессирования заболевания: хроническую фазу (ХФ) и терминальную фазу бластной трансформации. БФ, наряду с опухолевой пролиферацией и интоксикацией, характеризуется наличием в периферической крови или в костном мозге 20% и более бластных клеток [45-47].

Наиболее характерными признаками ХФ являются изменения в гемограмме (лейкоэритробластоз, постепенный сдвиг в нейтрофильном и эритроидном ряду до молодых форм с наличием промежуточных форм созревания), увеличение размеров печени и селезенки, наличие симптомов опухолевой интоксикации (лихорадка, потеря массы тела, профузные поты).

После открытия патогенетической роли мутаций в генах JAK2 и CALR для диагностики ПМФ используются следующие критерии [35,44,57]:

Большие критерии:
1. Пролиферация и атипия мегакариоцитов, сопровождаемая ретикулиновым и/или коллагеновым фиброзом 2-й или 3-й степени.
2. Несоответствие критериям ВОЗ для диагностики хронического миелолейкоза, истинной полицитемии, миелодиспластического синдрома или других МПЗ.
3. Обнаружение мутаций в генах JAK2, CALR, MPL или, при отсутствии этих мутаций, наличие другого клонального маркера.
Малые критерии:
1. Анемия, не вызванная сопутствующим заболеванием.
2. Лейкоцитоз $\geq 11x10^9$/л.
3. Пальпируемая селезенка (спленомегалия).
4. Повышение сывороточной активности лактатдегидрогеназы.

Для диагностики ПМФ необходимо наличие всех 3 больших критериев и, по крайней мере, одного малого критерия [36,41,53,58].

По данным трепанобиоптата в зависимости от степени выраженности фиброза костного мозга различают префиброзную и фиброзную стадии заболевания [17,24]. Трансформация префиброзной стадии в фиброзную наблюдается у 65% больных в течение 4,2 лет, трансформация в острый лейкоз отмечается в 5-30% случаев [16]. Продолжительность жизни больных ПМФ на 31% меньше, чем в популяции того же пола и возраста. Средняя продолжительность жизни составляет 5 лет, однако более молодые пациенты могут жить дольше [1,36,41,53].

Для определения вероятной продолжительности жизни больных ПМФ существует Международная шкала оценки прогноза (International Prognostic Scoring System – IPSS, 2009 г.), которая включает факторы, достоверно влияющие на выживаемость больных: возраст, уровень гемоглобина, процент бластов в периферической крови и наличие симптомов опухолевой интоксикации [12]. Для точной оценки индивидуального прогноза больного каждому из вышеуказанных признаков присваивается по одному баллу. Оценка прогноза IPSS позволяет определить вероятную ОВ в момент установления диагноза и четыре группы риска: низкий, промежуточный-1, промежуточный-2 и высокий. В последующем (2010 г.) система IPSS была модифицирована с присвоением двух баллов вместо одного балла фактору уровня гемоглобина менее 100 г/л и изменением классификации по группам риска соответственно баллам: 0 баллов – низкий риск; 1 или 2 балла – промежуточный-1; 3 или 4 – промежуточный-2; 5 или 6 баллов – высокий риск. Шкала именуется Dynamic International Prognostic Scoring System (DIPSS) и позволяет предсказывать риск бластной трансформации в любой момент подсчета, а не только при установлении диагноза [22,29].

Анализ многоцентровых исследований показал, что достоверными факторами являются также зависимость от гемотрансфузий, тромбоцитопения менее $100x10^9$/л и неблагоприятный кариотип [50]. Новая система стратификации, получившая название Dynamic International Prognostic Scoring System plus (DIPSS+) прогнозирует не только ОВ, но и время наступления бластной трансформации [14]. Согласно системе DIPSS+ учитываются следующие признаки: тромбоцитопения менее $100x10^9$/л, зависимость от гемотрансфузий и неблагоприятный кариотип (+8, -7/7q-, (17q), inv(3), -5|5q-, 12p-, перестройки 11q23) [15,19,39,40]. Каждому признаку присваивается соответствующий балл и оценивается прогностический риск: низкий (0 баллов), промежуточный-1 (1 балл), промежуточный-2 (2 балла), высокий (3 балла).

В 2014 г. разработана Международная мутационная прогностическая шкала Mutation-Enhanced International Prognostic Scoring System (MIPSS), которая также используется для определения как общей, так и быстропрогрессивной выживаемости при ПМФ [18,49,50,52]. Данная шкала обладает самой высокой степенью прогнозирования выживаемости в сравнении с предыдущими шкалами. При обследовании больного для определения риска по шкале MIPSS достаточно сбора анамнеза и забора проб крови для молекулярно-генетического исследования.

Целью лечения больных ПМФ является сдерживание прогрессирования заболевания и купирование его симптомов для улучшения качества жизни больных. При хронической фазе проводится либо циторедуктивная терапия, либо лечение с помощью интерферона в виде монотерапии или при комбинированном их использовании. В фазе бластного криза ПФМ – лечение по программам терапии острых лейкозов с учетом возраста и сопутствующих заболеваний.

С целью определения адаптированной терапии при ПМФ необходима стратификация больных с определением группы риска по системам IPSS, DIPSS, DIPSS+, MIPSS [10,12,14,18,29,49,50]. Так, при низком и промежуточном-1 рисках применение агрессивных методов лечения сопряжено с большим числом побочных эффектов. При отсутствии симптомов интоксикации и осложнений оправдано только динамическое наблюдение и симптоматическое лечение в виде коррекции анемии и тромбоцитопении, купирования симптомов опухолевой интоксикации. Пациентам моложе 60 лет без выраженной сопутствующей патологии в течение 1-2 лет от начала заболевания можно рассматривать возможность проведения аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК). При быстропрогрессирующей спленомегалии показана циторедуктивная терапия гидроксимочевиной или интерферонами; при неэффективности стандартной цитостатической терапии применяются ингибиторы JAK2 (руксолитиниб) в течение 3-6 месяцев. Больным с промежуточным-2 и высоким риском по шкале DIPSS и DIPSS+, медиана общей выживаемости которых составляет 35 и 16 месяцев, соответственно, наиболее оправдано проведение алло-ТГСК [13,32,51]. Результаты алло-ТГСК зависят от стадии заболевания и группы риска на момент трансплантации. Так, 5-летняя ОВ после ТГСК у больных в группе низкого риска составляет 76%, в группе промежуточного-1 – 48%, промежуточного-2 и высокого – 38%, а у больных с трансформацией в ОМЛ 2-летняя ОВ составляет около 40% [6,20].

В последние два года для стратификации больных ПМФ предложены новые прогностические шкалы: MIPSS70, MIPSS70+ версия 2.0 и GIPSS, в которые включены такие компоненты как мутации, кариотипы и уровни гемоглобина с учетом половой принадлежности [10,25,33,37,38,54].

Таким образом, факторами, влияющими на выбор варианта лечения, являются:

- группа риска по системам IPSS, DIPSS, DIPSS+, MIPSS, MIPSS70, MIPSS70+ версия 2.0 и GIPSS;
- наличие и степень выраженности симптомов опухолевой интоксикации и пролиферации (особенно спленомегалии);
- возраст больного;
- наличие совместимых по системе HLA доноров для возможного выполнения аллогенной трансплантации костного мозга.

Следует отметить, что алло-ТГСК является эффективным методом лечения ПМФ, способствующим достижению полного гематологического, цитогенетического и молекулярного ответов. Однако, с учетом возраста больных и наличия сопутствующих заболеваний, этот метод лечения применяется лишь у ограниченного числа пациентов. Поэтому основным методом лечения больных ПМФ остается медикаментозная терапия, позволяющая сдерживать прогрессирование заболевания. В хронической фазе ПМФ проводится циторедуктивная терапия гидроксикарбамидом (гидреа), цитарабином (цитозар), которые назначаются в качестве монотерапии в малых дозах. Так, гидреа применяется в дозе 10-40 мг/кг/сут, цитозар – 10-20 мг/м^2/сут 10-14 дней каждого месяца. Интерфероны (интрон А, роферон) применяются в режимах как монотерапии, так и в сочетании с цитостатиками. С целью стимуляции эритропоэза и уменьшения необходимости в трансфузиях эритроцитов используются эритропоэзстимулирующие средства (рекормон, эритростим). Препараты применяются в стандартных дозах по 150 МЕ/кг 3 раза в неделю, 40 000 МЕ 1 раз в неделю или дарбэпоэтин 500 мкг 1 раз в 3-4 недели.

При лечении больных ПМФ применяются также глюкокортикоидные препараты, которые снижают секрецию цитокинов, уменьшают пролиферацию фибробластов и образование соединительной ткани, что способствует уменьшению симптомов опухолевой интоксикации. Преднизолон назначается в дозе 0,5 мг/кг/сут или 15-30 мг/сут с постепенным уменьшением до минимально эффективной [1,3]. Для лечения больных ПМФ применяют также иммуномодуляторы, которые регулируют иммунную систему путем торможения активности цитокиновых сигнальных путей и блокируют ангиогенез. К ним относятся талидомид, леналидомид и другие. Так, например, леналидомид (ревлимид) назначается в дозе 10-25 мг ежедневно в течение 21 дня 25-дневного цикла. Его комбинация с преднизолоном или дексаметазоном повышает эффективность лечения и снижает токсичность.

В последние годы применяется ингибитор янускиназ JAK2 руксолитиниб (Джакави) - препарат прицельного таргетного действия, направленный на ключевое звено патогенеза ПМФ – сигнальный путь JAK-STAT. Начальная доза Джакави составляет 15 мг 2 раза в день при количестве тромбоцитов 100-200x10^9/л и 20 мг 2 раза в день при количестве тромбоцитов более 200x10^9/л.

При массивной спленомегалии с синдромом гиперспленизма, компрессией внутренних органов и сосудов и недостаточном эффекте медикаментозной терапии, нарастающей кахексии показана спленэктомия [23,30]. Длительное увеличение размеров печени и селезенки с очагами экстрамедуллярного кроветворения нередко приводит к развитию портальной гипертензии, требующей хирургического вмешательства (наложение портальных анастомозов). При выраженной спленомегалии применяется также лучевая терапия [39,55]. Среди средств сопроводительной терапии чаще проводится компонентная гемотерапия (трансфузии эритроцитов и тромбоцитов), андрогены, дезагреганты.

Приводим одно из наших наблюдений. Больной Т., 53 года. В декабре 2012 года впервые стал отмечать тяжесть и болевые ощущения в левом подреберье, увеличение объёма живота, потливость и общую слабость (рис. 1).

Обратился в поликлинику по месту жительства, где заподозрено миелопролиферативное заболевание, после чего пациент направлен в гематологический стационар. Из анамнеза выяснено, что пациент служил в ракетных войсках в Афганистане (1979-1980 гг.), перенес болезнь Боткина (1985 г.), злоупотреблял алкоголем и состоял на диспансерном учете у гастроэнтеролога с диагнозом: цирроз печени, класс «В» по Чайлд-Пью. Осмотр показал состояние больного средней степени тяжести. Кожа и видимые слизистые бледные, геморрагий нет. Со стороны сердечно-сосудистой и дыхательной систем патологии не выявлено. Живот увеличен в объеме за счет гепатоспленомегалии. Периферических отеков не имеется.

В общем анализе крови (ОАК) от 14.01.2013: гемоглобин - 89 г/л; эритроциты - 3,36x10^{12}/л; лейкоциты - 23,1x10^9/л;

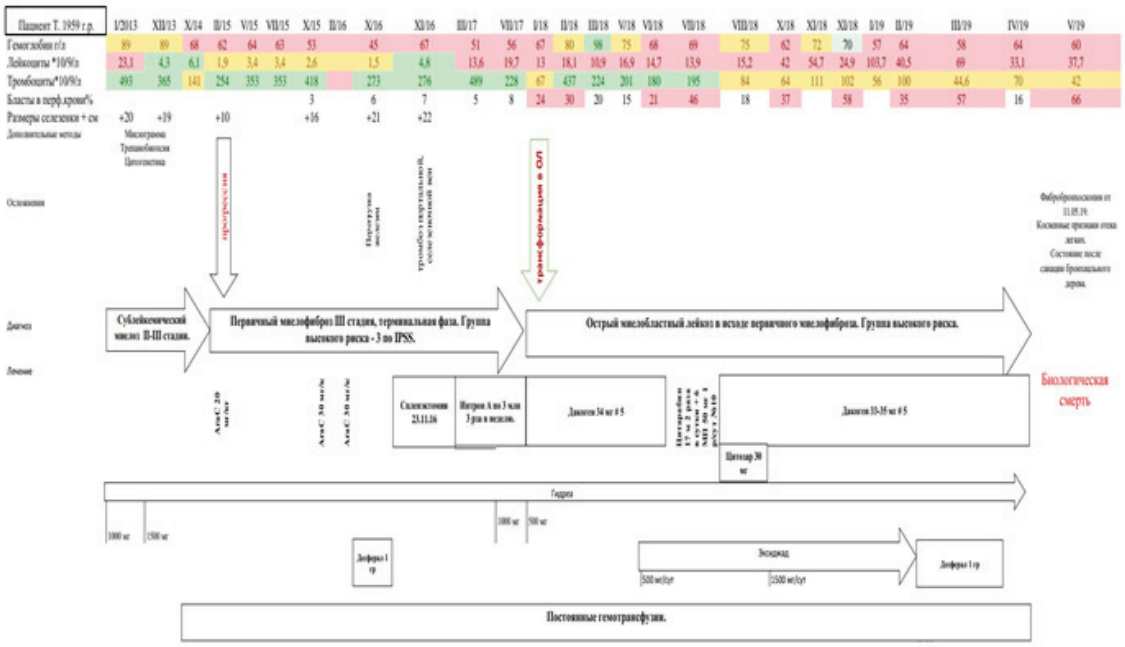

Рис.1. График анамнеза больного Т., 53 года

п/я - 15%; с/я - 50%; лимфоциты - 6%; моноциты - 4%; миелоциты - 18%; метамиелоциты - 4%; базофилы - 3%, тромбоциты - 679x10^9/л; СОЭ - 38 мм/ч. Повышение уровня лактатдегидрогеназы (ЛДГ) – 2053 ед/л в биохимическом анализе крови.

При УЗИ органов брюшной полости от 15.01.2013: высота правой доли печени 176 мм, толщина 135 мм. Высота левой доли печени 103 мм, толщина 66 мм. Контуры печени ровные. Эхоструктура однородная. Эхоплотность повышена. Портальная вена 13 мм. Желчный пузырь овальной формы. Стенка пузыря без особенностей. В полости пузыря эхогенное содержимое. Общий желчный проток 4 мм. Поджелудочная железа не увеличена. Контуры железы ровные. Эхоструктура однородная. Эхоплотность средняя. Селезеночная вена 9 мм. Селезенка увеличена, 200x78 мм. Контур ровный. Эхоструктура однородная. В области ворот селезенки добавочная доля диаметром 24 мм. Заключение: диффузные изменения в паренхиме печени. Гепатоспленомегалия. Хронический пиелонефрит. Нефроптоз слева. Добавочная доля селезенки.

Данные миелограммы от 15.01.2013: бласты – 3%; нейтрофильные миелоциты – 12,7%; нейтрофильные метамиелоциты - 4%; п/я - 26,7%; с/я - 42%; все нейтрофилы -85,4%; индекс созревания нейтрофилов 0,1 усл.ед.; все эозинофилы - 0,8%; все базофилы - 2,0%; моноциты - 0,2%; все лимфоциты - 6,3%; все клетки лейкоцитарного ряда - 94,7%; нормоциты базофильные - 0,3%; нормоциты полихроматофильные - 0,2%; нормоциты оксифильные - 1,8%; все клетки эритроидного ряда - 2,3%; индекс созревания эритрокариоцитов - 1,1 усл.ед.; лейкоэритробластическое отношение 41:1 усл.ед. Заключение: костный мозг клеточный, полиморфный. Тип кроветворения нормобластический. Эритроидный росток резко сужен. Миелоидный росток гиперплазирован за счет зрелых форм нейтрофилов. Увеличено количество базофилов. Мегакариоцитов при осмотре не обнаружено.

Гистологическое исследование трепанобиоптата подвздошной кости от 17.01.2013 №9695: в препаратах костный мозг. Жировой компонент отсутствует. Отмечается значительное сужение всех ростков за счет разрастания соединительной ткани как в виде полей фиброза, так и в виде рубцовой соединительной ткани. Единичные незрелые глыбки остеоида. Множество мегакариоцитов среднего размера и мельче, с приемлемой активностью. Среди клеток «белого ряда» значительно преобладают гранулоциты, встречаются метамиелоциты, много сегментированных клеток; лимфоцитов мало. Заключение: морфологическая картина более характерна для миелоидного фиброза (рис. 2,3,4,5).

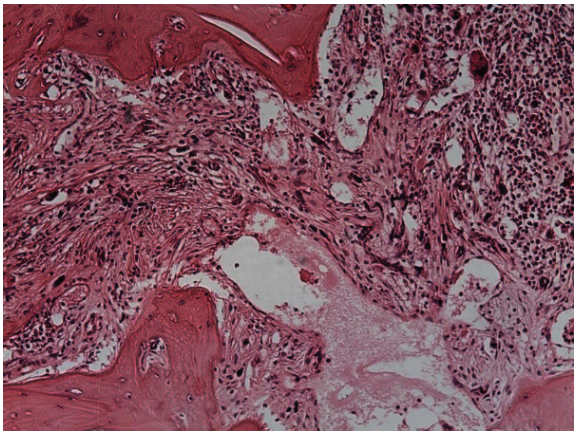

Рис. 2. Коллагеновый фиброз в одной из пазух. Гематоксилин-эозин. Увеличение x100.

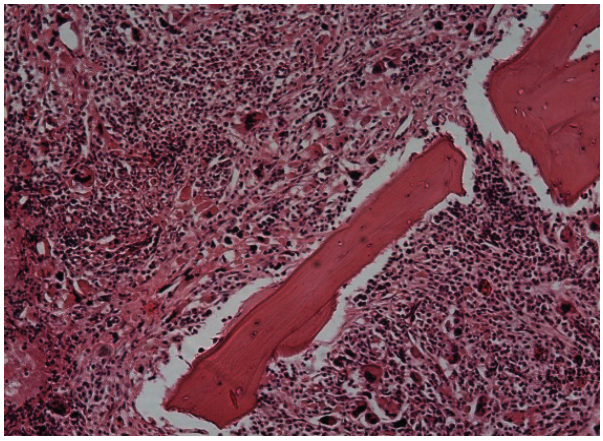

Рис.3. Паратрабекулярное расположение мегакариоцитов. Гематоксилин-эозин. Увеличение x100

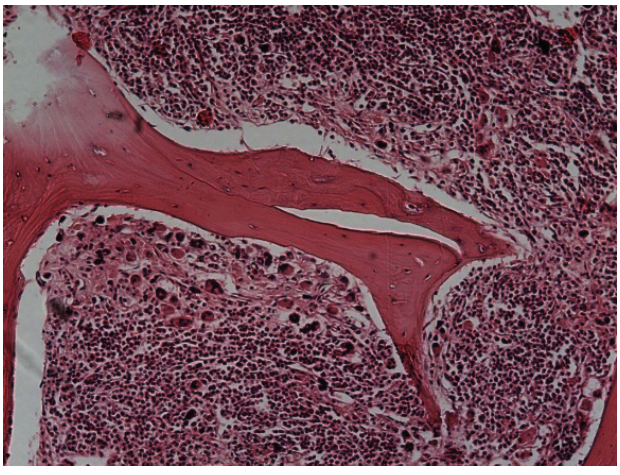

Рис. 4. Паратрабекулярное расположение крупных мегакариоцитов в виде кластера. Гематоксилин-эозин. Увеличение x100

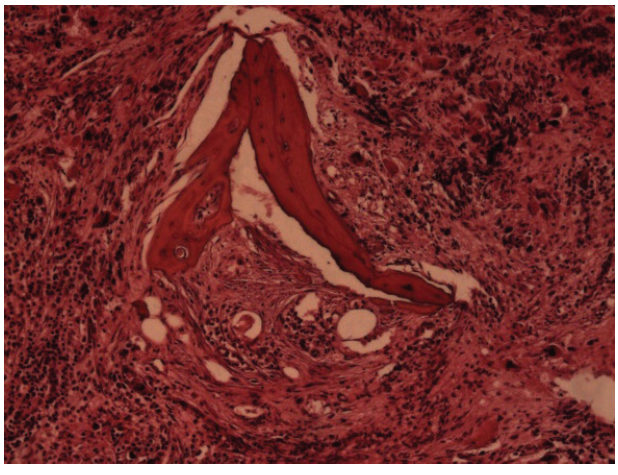

Рис. 5. Очаг остеомиелосклероза. Гематоксилин-эозин. Увеличение x100

Цитогенетическое исследование костного мозга от 26.01.13: в исследованных клетках костного мозга хромосомной патологии не выявлено. Однако, генетическое исследование методом аллельспецифической полимеразной цепной реакции в режиме реального времени на обнаружение мутации V617F в гене JAK2 показало наличие гетерозиготной мутации GT (ген JAK2, rs 77375493). Данная мутация ассоциирована с повышением риска тромбозов при наличии миелопролиферативных заболеваний [57].

На основании полученных данных обследования установлен диагноз: «первичный миелофиброз, хроническая фаза; промежуточный риск-2 по шкале DIPSS+» и начата терапия гидроксимочевиной в дозе 1500 мг/с. Пациент в удовлетворительном состоянии выписан для продолжения лечения в амбулаторных условиях.

При выписке из стационара в ОАК - гемоглобин 83 г/л; эритроциты 3,08x10^{12}/л; лейкоциты 8,8x10^{9}/л; тромбоциты 493x10^{9}/л; миелоциты - 2%; п/я - 11%; с/я - 71%; базофилы - 5%; эозинофилы - 1%; моноциты - 1%; лимфоциты - 9%; нормоциты 5:100.

Повторная госпитализация через 10 месяцев в декабре 2013 года в связи с ухудшением состояния: выраженная слабость, боли в левом подреберье, несмотря на прием гидроксимочевины. В ОАК - гемоглобин 89 г/л; эритроциты 2,7x10^{12}/л; лейкоциты 4,3x10^{9}/л; п/я - 4%; с/я - 62%; эозинофилы - 3%; базофилы - 3%; моноциты - 3%; лимфоциты - 25%; тромбоциты 365x10^{9}/л; СОЭ - 18 мм/час.

УЗИ органов брюшной полости от 25.12.2013: диффузные изменения печени. Спленомегалия 190x90x130 мм. Хронический холецистит. Нефроптоз слева: смещенте на 7-8 см.

Миелограмма от 28.12.2013: костный мозг малоклеточный. Подсчет на 100 клеток: п/я 4%; с/я 75%; лимфоциты 20%; моноциты 1%. Вероятно разведен периферической кровью.

Гистологическое исследование трепанобиоптата подвздошной кости №3381-83 от 07.12.2013: в препаратах – костный мозг с неравномерным разрастанием фиброретикулярной стромы, местами вплоть до полной облитерации костно-мозгового пространства. Трабекулы кости утолщены, с неровными линиями, склеиваются. Миелоидные элементы находятся на разных стадиях созревания, относительно много бластных клеток. Уменьшено содержание лимфоидных элементов. Количество мегакариоцитов увеличено, достигает 30-35 в поле зрения, видны как в склерозированных участках, так и в зонах малой клеточности. Величина их небольшая, форма в основном округлая, отшнуровка тромбоцитов малочисленная. Эритропоэз угнетен, но прослеживаются все промежуточные клетки роста (рис. 6,7).

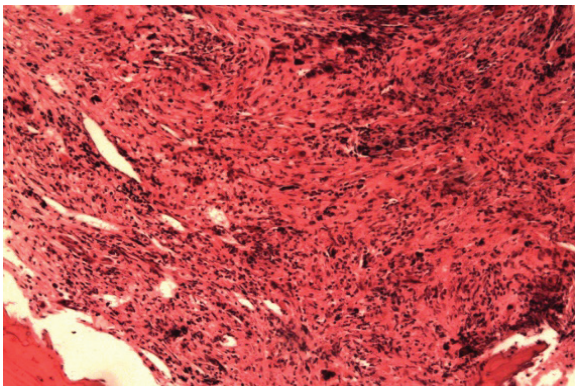

Рис. 6. Клетки костного мозга расположены среди коллагеновых волокон. Гематоксилин-эозин. Увеличение x100

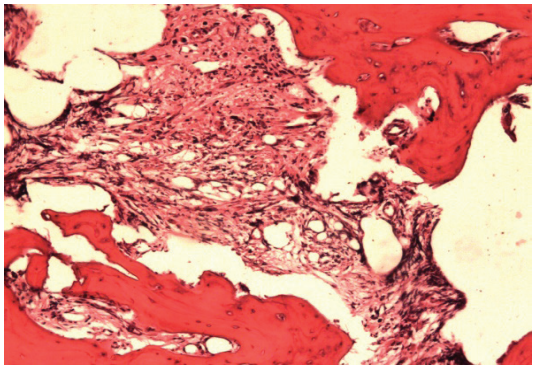

Рис. 7. Выраженный миелофиброз. Гематоксилин-эозин. Увеличение x100

На фоне приема гидроксимочевины в дозе 1500 мг/сут, дезагрегантной терапии (тромбо АСС 100 мг/с) размеры селезенки уменьшились до 14x10 см, повысился уровень гемоглобина до 95 г/л; количество лейкоцитов 4,7x10^{9}/л; наблюдался тромбоцитоз 408x10^{9}/л;

Спустя 9 месяцев вновь госпитализация в связи с анемией (уровень гемоглобина 62 г/л, количество эритроцитов 2,1x10^{12}/л) и тромбоцитопенией (141x10^{9}/л). Размеры печени и селезенки выступают из под реберного края на 4 см и 10 см, соответственно. Начат курс химиотерапии малыми дозами цитозин-арабинозида (20 мг/кг) в течение 21 дня, гемотрансфузии. Выписан с незначительным улучшением и рекомендацией продолжения лечения гидроксимочевиной в дозе 1500 мг/сут. В последующем частые госпитализации в связи с неуклонным прогрессированием заболевания, сопровождающимся тяжелым анемическим синдромом и зависимостью от гемотрансфузий.

В ноябре 2015 г. госпитализирован по экстренным показаниям: в ОАК от 05.11.2015: гемоглобин 53 г/л; эритроциты 1,6x10^{12}/л; лейкоциты 2,6x10^{9}/л; тромбоциты 67,0x10^{9}/л; СОЭ 25 мм/час. Микроскопия: бласты 3%; миелоциты 4%; метамиелоциты 1%; п/я - 13%; с/я - 56%; эозинофилы - 1%; базофилы - 1%; моноциты -5%; лимфоциты - 16%. Вновь проведен курс лечения цитозаром в дозе 30 мг/кг (№11), трансфузии эритроцитарной массы. Отмечен положительный эффект в виде уменьшения размеров селезенки с +16 до +8 см; печени с +6 см до +3 см. Поддерживающая химиотерапия продолжалась гидроксимочевиной в дозе 1500 мг/сут. В феврале проведен очередной курс химиотерапии малыми дозами цитозара, после которого пациент в течение шести месяцев не обращался и только в октябре 2016 г. госпитализирован в тяжелом состоянии с глубокой анемией и выраженной спленомегалией, занимающей всю левую половину брюшной полости (+21 см). При поступлении ОАК показал: гемоглобин 45 г/л; лейкоциты 1,53x10^{9}/л; тромбоциты 20,0x10^{9}/л; СОЭ 60 мм/час. Микроскопия: бласты 6%; метамиелоциты - 1%; п/я - 12%; с/я - 38%; эозинофилы - 1%; базофилы - 3%; моноциты - 8%; лимфоциты - 31%; эритронормобласты - 1:100.

В связи с угрозой разрыва селезенки и тяжелой гемотрансфузионной зависимостью проведена спленэктомия (23.11.2016). Макропрепарат: 45x20x10 см, плотная, неровная. Вес – 2600 мг. Операция осложнилась пристеночным тромбозом портальной и селезеночной вен. Проводилась антикоагулянтная, дезагрегантная и поддерживающая химиотерапия гидроксимочевиной в суточной дозе 1500 мг.

На этом этапе наблюдения констатирована терминальная

фаза первичного миелофиброза, группа высокого риска - 3 по DIPSS+. Состояние после спленэктомии. Осложнения: посттрансфузионная перегрузка железом. Пристеночный тромб портальной и селезеночной вен.

С декабря 2016 г. к терапии гидроксимочевиной добавлен альфа-интерферон по 3 млн 3 раза в неделю. В марте 2017 г. – срочная госпитализация в связи с тяжелой анемией (Hb - 51 г/л) и тромбоцитозом (589x10^9/л). Количество лейкоцитов - 13,6x10^9/л; СОЭ – 45 мм/час; микроскопия: бласты - 5%; метамиелоциты - 3%; п/я - 3%; с/я - 27%; эозинофилы - 1%; моноциты - 6%; лимфоциты - 55%.

Ультразвуковая допплерография сосудов печени от 05.04.17г.: Гепатомегалия. Кровоток в портальной вене не нарушен. Гемодинамических стенозов, тромбозов не выявлено. Проводились трансфузии эритроцитарной массы, интрон А по 3 млн 3 раза в день. Выписан с рекомендациями продолжить прием гидроксимочевины 1500 мг, интрон А.

С июля 2017 г. по январь 2018 г. пациент находился на амбулаторном наблюдении и получал комбинированную терапию гидроксимочевиной с альфа-интерфероном. В связи с ухудшением состояния неоднократно госпитализирован в гематологическое отделение многопрофильной больницы №1 г. Нур-Султан. В ОАК от 08.01.2018: гемоглобин 69 г/л; лейкоциты 13,0x10^9/л; тромбоциты 67,0x10^9/л, СОЭ 39 мм/час. Микроскопия: бласты - 30%; миелоциты - 34%; п/я - 3%; с/я - 13%; эозинофилы - 1%; базофилы - 1%; моноциты - 8%; лимфоциты - 10%; нормоциты 476:100. В связи с трансформацией первичного миелофиброза в острый миелобластный лейкоз назначены курсы лечения децитабином (дакоген 34,5 мг) ежемесячно на фоне гемотрансфузионной и хелатной терапии эксиджадом по 500 мг х 2 раза в день. Проведено 12 курсов химиотерапии децитабином. Достигнуто лишь клиническое улучшение: несколько уменьшались размеры печени, потливость и слабость. В перерыве от курсового лечения проводилась поддерживающая химиотерапия гидроксимочевиной (500 мг 1 раз в сутки).

Последняя госпитализация в связи с ухудшением состояния 10.05.2019, когда появились боли в костях, одышка, сердцебиение и выраженная слабость. Бригадой скорой помощи доставлен в приемный покой многопрофильной больницы № 1 г. Нур-Султан. В ОАК: гемоглобин 60 г/л; тромбоциты 42,0x10^9/л; лейкоциты 37,7x10^9/л; бласты 66%; п/я - 5%; с/я - 21%; моноциты - 2%; лимфоциты - 6%; СОЭ 52 мм/час. В связи с тяжестью состояния больной экстренно госпитализирован в гематологическое отделение. При осмотре состояние крайне тяжелое. Кожные покровы бледно-землистого цвета. ЧДД - 24 в мин. Аускультативно в легких дыхание везикулярное, влажные хрипы в задне-нижних отделах грудной клетки. Сатурация без кислорода 85%, на кислороде 97%. Тоны сердца ослабленной звучности, тахикардия ЧСС 120 в мин, АД 80/50 мм рт. ст. Живот увеличен в объёме за счет гепатомегалии и асцита. 11.05.2019 в 18:55 в связи с нарастающей сердечно-сосудистой и дыхательной недостаточностью переведен в реанимационное отделение. Фибробронхоскопия от 11.05.2019 - косвенные признаки отека легких. Состояние после санации бронхиального дерева.

Состояние больного прогрессивно ухудшалось и, несмотря на интенсивную реанимационную терапию, наступила остановка сердечной деятельности, в 19:10 констатирована биологическая смерть.

Интерес представленного клинического случая заключается в том, что несмотря на своевременную диагностику ПМФ с установлением промежуточного риска-2 в соответствии со шкалой DIPSS+, проведение спленэктомии и выявление гетерозиготной мутации в гене JAK2, трансформация в острый лейкоз у больного Т., 53 лет наступила достаточно рано.

Таким образом, существующие на сегодняшний день методы лечения пациентов с ПМФ направлены лишь на сдерживание прогрессирования заболевания, профилактику осложнений и купирование симптомов болезни. Единственным радикальным способом лечения больных первичным миелофиброзом является аллогенная трансплантация гемопоэтических стволовых клеток, использование которой сопряжено с высоким риском летальности и осложнений. –

Для улучшения выживаемости больных ПМФ рекомендуется проведение молекулярно-генетической верификации заболевания и стратификации с использованием Международной шкалы оценки прогноза DIPSS+ для выбора тактики лечения.

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SUMMARY

CLINICAL, MORPHOLOGICAL AND MOLECULAR GENETIC FEATURES AND PROGNOSTIC FACTORS OF PRIMARY MYELOFIBROSIS. A CASE OF PRIMARY MYELOFIBROSIS TRANSFORMATION INTO ACUTE MYELOID LEUKEMIA

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Primary myelofibrosis is a common disease from the group of Ph-negative myeloproliferative diseases. The article presents modern data on the pathogenesis of Ph-negative myeloproliferative diseases, as well as diagnostic criteria, treatment tactics and prognosis factors for primary myelofibrosis. A clinical case of transformation of primary myelofibrosis into acute myeloid leukemia is described.

Purpose of the study - to present up-to-date information on the pathogenesis, diagnostic criteria, principles of treatment and prognostic factors of primary myelofibrosis, as well as to present a clinical case of transformation of primary myelofibrosis into acute myeloblastic leukemia.

According to modern concepts, for the early diagnosis of primary myelofibrosis, along with the clinical and morphological methods of examining patients, molecular genetic verification of the disease is extremely important. To improve the survival rate of patients with primary myelofibrosis, molecular genetic verification of the disease and stratification for the choice of treatment tactics are necessary.

Keywords: primary myelofibrosis, diagnostic criteria, prognostic factors, stratification, treatment tactics

РЕЗЮМЕ

КЛИНИКО-МОРФОЛОГИЧЕСКИЕ И МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ ПЕРВИЧНОГО МИЕЛОФИБРОЗА И ФАКТОРЫ ПРОГНОЗА. ОПИСАНИЕ СЛУЧАЯ ТРАНСФОРМАЦИИ ПЕРВИЧНОГО МИЕЛОФИБРОЗА В ОСТРЫЙ МИЕЛОБЛАСТНЫЙ ЛЕЙКОЗ

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Первичный миелофиброз – часто встречающееся заболевание из группы Ph-негативных миелопролиферативных заболеваний. В статье представлены современные данные о патогенезе Ph-негативных миелопролиферативных заболеваний, а также диагностические критерии, тактика лечения и факторы прогноза первичного миелофиброза. Описан клинический случай трансформации первичного миелофиброза в острый миелобластный лейкоз.

Цель исследования - представить современные сведения о патогенезе, критериях диагностики, принципах лечения и прогностических факторах первичного миелофиброза, а также описать клинический случай трансформации первичного миелофиброза в острый миелобластный лейкоз.

Согласно современным представлениям, для ранней диагностики первичного миелофиброза, наряду с клинико-морфологическими методами обследования пациентов, весьма значимым является молекулярно-генетическая верификация заболевания. Для улучшения выживаемости больных первичным миелофиброзом необходима молекулярно-генетическая верификация заболевания и проведение стратификации для выбора тактики лечения.

რეზიუმე

მიელოფიბროზის კლინიკურ-მორფოლოგიური და მოლეკულურ- გენეტიკური თავისებურებანი და პროგნოზის ფაქტორები. პირველადი მიელოფიბროზის მწვავე მიელობლასტურ ლეიკოზად ტრანსფორმაციის შემთხვევის აღწერა

ს ბაიდურინი, ფ. ბეკენოვა, გ. რახიმბეკოვა, ბ. აბდულინა, ა. ნაკიში

ასს "ასტანის სამედიცინო უნივერსიტეტი", შინაგანი სნეულებათა კათედრა ნეფროლოგიის, ჰემატოლოგიის, ალერგოლოგიისა და იმუნოლოგიის კურსით, ნურსულტანი, ყაზახეთი

პირველადი მიელოფიბროზი წარმოადგენს ხშირ დაავადებას Ph-ნეგატიური მიელოპროლიფერაციული

დაავადებების ჯგუფიდან. სტატიაში წარმოდგენილია თანამედროვე მონაცემები Ph-ნეგატიური მიელოპროლიფერაციული დაავადებების პათოგენეზის შესახებ, აგრეთვე დიაგნოსტიკური კრიტერიუმები, მკურნალობის ტაქტიკა და პირველადი მიელოფიბროზის პროგნოზის ფაქტორები. აღწერილია პირველადი მიელოფიბროზის მწვავე მიელობლასტურ ლეკოზად გარდაქმნის კლინიკური შემთხვევა.

კვლევის მიზანი - თანამედროვე და რეტროსპექტული ლიტერატურის ანალიზი პირველადი მიელოფიბროზის პათოგენეზის,დიაგნოსტიკის,მკურნალობის პრინციპებისა და პროგნოზული ფაქტორების შესახებ და პირველადი მიელოფიბროზის მწვავე მიელობლასტურ ლეკოზად გარდაქმნის კლინიკური შემთხვევის აღწერა.

თანამედროვე წარმოდგენების თანახმად, პირველადი მიელოფიბროზის ადრეული დიაგნოსტირებისთვის, პაციენტთა გამოკვლევის კლინიკურ-მორფოლოგიურ მეთოდებთან ერთად, ძალზე მნიშვნელოვანია დაავადების მოლეკულურ-გენეტიკური ვერიფიკაცია. პირველადი მიელოფიბროზით დაავადებულთა გადარჩენილობის გასაუმჯობესებლად აუცილებელია დაავადების მოლეკულურ-გენეტიკური ვერიფიკაცია და მკურნალობის ტაქტიკის ასარჩევად სტრატიფიკაციის ჩატარება.

LPL AND ADRB2 GENE POLYMORPHISMS: RELATIONSHIP WITH LIPIDS AND OBESITY IN KAZAKH ADOLESCENTS

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Adolescent obesity is recognized as one of the biggest public health concerns. According to the World Health Organization in the world in 2016, 340 million children and adolescents aged 5 to 19 years were overweight or obese. The prevalence of overweight and obesity among children and adolescents aged 5 to 19 years has risen sharply from 4% in 1975 to over 18% in 2016. In 2018, an estimated 40 million children under the age of 5 years are overweight or obese [1]. In Kazakhstan, as shown by the epidemiological monitoring of childhood obesity, the situation is even slightly worse than the global average. According to the state health development program of the Republic of Kazakhstan for 2020-2025 among Kazakhstani teenagers (children from 10 to 19 years), 5% are obese and 20% of children are overweight. Risk factors for adolescent and childhood obesity include genetics, environmental factors, and excessive consumption of fast food, decreased physical activity, and family stress [2]. Given the alleged heritability of BMI, genetic approaches can be a useful tool for analyzing mechanisms related to weight regulation and understanding susceptibility to obesity [3].

Genetic predisposition has a fundamental role in the development of obesity and overweight. The 12th version of the human obesity gene map includes more than 600 genes, genetic markers, and chromosome regions directly or indirectly associated with the phenotype of obesity [4]. The mechanisms of the formation of cardiovascular pathology in obesity are associated with hormonal and metabolic abnormalities caused by the accumulation of adipose tissue.

The key role among them is played by the development of insulin resistance (IR) of compensatory hyperinsulinemia, being a link between impaired glucose tolerance, arterial hypertension, and dyslipidemia [5]. In addition, insulin resistance and dyslipidemia are often observed in obese individuals already in childhood [6].

The genes that form the polygenic system individually give a weak effect, only determine the tendency to excessive accumulation of adipose tissue, and the degree of manifestation depends on environmental factors [7]. In this regard, the study of the relationship of genetic factors determining the predisposition to the development of the main disorders characteristic of obesity by a complex of clinical, metabolic and environmental factors in obese adolescents is of particular relevance. A promising direction is the study of the structural features of genes involved in lipid metabolism disorders (*LPL/S447T*) and the risk of diabetes and obesity (*ADRB2/Gln27Glu*).

Lipoprotein lipase (*LPL*) catalyzes the hydrolysis of triglycerides from circulating very low density lipoproteins and chylomicrons and delivers derivatives of fatty acid lipoproteins to adipose tissues for storage or oxidation in muscles [8]. Mutations in the LPL or pathological LPL lead to hypertriglyceridemia, dyslipidemia, which lead to various disorders, such as coronary heart disease, hypertension, and obesity [9].

Type 2 beta-adrenergic receptors (*ADRB2*) stimulate lipolysis in fat cells [10] and are involved in mobilizing fat from fat cells to produce energy in response to hormones (adrenaline, norepinephrine) and stimulate glycogenolysis to meet energy needs. The Glu27 allele tends to increase body mass index, body fat mass and type 2 diabetes, as well as to suppress lipid oxidation [11]. The amino acid replacement of Gln27Glu in the *ADRB2* gene leads to receptor resistance to agonists, which is accompanied by hypertriglyceridemia and obesity [12].

In an obese state, adipose tissue undergoes a constant excess of energy, so that over time the ability of this tissue to accumulate lipids can be exceeded, and adipose tissue that can respond to this excess can reduce the expression of genes involved in the processing and storage of lipids. If this happens, adipose tissue may begin to work incorrectly, which over time will lead to metabolic disorders.

Thus, the aim of this study was to study the effect of polymorphisms of the *LPL* gene and *ADRB2* gene on body weight and lipid spectrum in adolescents of Kazakh nationality.

Material and methods. In total, 184 adolescents of Kazakh nationality aged 15 to 18 years old who were studying in high school in Semey were selected by random sampling. The main group included 70 overweight adolescents (BMI>23.5), and the control group included 114 adolescents with normal physique (BMI≤23.4). The inclusion criteria in the study were age, overweight for the main group and face (BMI>23,5), with normal weight (BMI<23,4) for the control group. The determination of body mass index (BMI) was calculated by the formula body weight (kg)/height (m^2). Waist circumference and hip circumference were also measured. The study did not include adolescents with diabetes mellitus, hormone therapy, heart defects, and a history of malignant neoplasms, heart and/or kidney failure, mental illness, and congenital endocrine pathology.

DNA extraction was performed with QIAamp DNA Mini Kit (QIAGEN) kits. DNA was evaluated using a NanoDrop 1000 spectrophotometer (Thermo Scientific, Waltham, MA, USA) with wavelengths of 230, 260, and 280 nm. The isolated DNA was frozen and stored at -20°C. Genotyping was performed by real-time PCR using a CFX 96 instrument (Bio-Rad, CA, USA). A working mixture for amplification of rs1042714 and rs328 DNA polymorphisms in a total volume of 20 µl was prepared in the presence of TaqMan Genotyping Master mix and 5 µl of DNA. All reagents for amplification of Synthol production (Russia). The amplificatio program for the SNP genes *ADRB2* (rs1042714) and *LPL* (rs328) included preliminary denaturation at 95°C for 3 minutes, then 40 cycles of 95°C for 15 seconds and 65°C for 40 seconds.

The determination of the level of total cholesterol, LDL, HDL, triglycerides, glucose, and fasting blood serum was carried out by the chemiluminescent chain method using a Cobas Integra 400 plus biochemical analyzer (Roche Diagnostics, Switzerland). Specific proteins of apoA1, apoB and insulin in the blood serum were carried out in the Olympus Clinical Diagnostic Laboratory, which is the subject of accreditation according to ISO 15189: 2012. All reagents are Roche Diagnostics GmbH (Germany).

All adolescents participating in the study and their parents/egal representatives were introduced to the study objectives and upcoming procedures. All (parents/legal representatives) received informed written consent to participate in the study and the processing of personal data. The study was approved by the Local Ethics Committee of the Semey Medical University (meeting minutes No. 6 dated 06.16.2017) and meets the requirements of the Helsinki Declaration of the World Medical Association.

Statistical analysis was performed using the IBM SPSS Statistics Version 21 package (International Business Machines Corp., Armonk, NY, USA), and/or Microsoft Office Excel

For descriptive statistics of quantitative variables, Mann-Whitney or Kruskal-Wallis tests were used. Comparison of the frequencies of genotypic distributions between the groups used the $\chi 2$ criterion. The associative signal was characterized by the odds ratio (OR), its 95% confidence interval, and statistical significance (*p* value). Comparison between groups was performed using multivariate logistic regression analysis. Associative genetic analysis took into account age and sex data. Differences were considered statistically significant at $p<0.05$. The deviation of the frequencies of genotypes from Hardy-Weinberg equilibrium was evaluated using the $\chi 2$ test.

Results and discussion. In total, 184 adolescents of Kazakh nationality took part in the study, including boys n=62, girls n=122. Among boys, the average age was 16 (95%: 15.77-16.23) years, among girls the average age was 16.07 (95%: 15.90-16.23) years old.

The average BMI for boys was 23.61 (95%: 22.75-24.46), and for girls 22.01 (95%: 21.39-22.63). When comparing the average BMI by sex, it was found that in boys the BMI was significantly higher compared to girls (Mann – Whitney test=2746.5 *p*=0.002). When considering the average values of biochemical parameters between BMI groups, the difference in average values was revealed only in the levels of TG (*p*=0.011) and glucose (p=0.001). For other biochemical indicators, the difference in average values between BMI groups was not found.

The frequency of gene polymorphisms can be seen in table 1. The frequency of the CC, CG, GG genotypes of the rs1042714 polymorphism of the ADRB2 gene was 58%, 38%, 9%, respectively. And the frequency of the CC, CG, GG genotypes of the rs328 polymorphism of the LPL gene was 45%, 48%, 7%, respectively. Both polymorphisms did not deviate from the balance of the Hardy-Weinberg law.

When conducting a comparative analysis of the frequency distribution of the alleles and genotypes rs328 of the *LPL* gene and rs1042714 of the *ADRB2* gene with BMI groups, no statistically significant difference was revealed (table 2). When conducting multivariate logistic regression between the BMI groups and rs1042714 polymorphisms of the ADRB2 gene (*p*=0.58) and rs328 of the LPL gene (*p*=0.12), no relationship was found.

Table 1. The frequency of genotypes of polymorphisms of the ADRB2 and LPL genes among adolescents in the Kazakh population

SNP	Hardy-Weinberg P value	All	Age	Female	Male
ADRB2 (rs1042714)					
CC	0.69	106 (58%)	16.06 (9%)	73 (60.3%)	33 (52.4%)
CG		69 (38%)	15.99 (11%)	41 (33.9%)	28 (44.4%)
GG		9 (5%)	16.33 (33%)	7 (5.8%)	2 (3.2%)
LPL (rs328)					
CC	0.083	83 (45%)	16.18 (1%)	53 (43.8%)	30 (47.6%)
CG		89 (48%)	15.94 (1%)	59 (48.8%)	30 (47.6%)
GG		12 (7%)	15.83 (21%)	9 (7.4%)	3 (4.8%)

Table 2. Comparative analysis of the frequency distribution of alleles and genotypes for 2 gene polymorphisms among adolescents of the Kazakh population with a body mass index

Alleles and genotypes	Allele and genotype frequency		p	CI	95%OR
	BMI> 23,5 (n=70)	BMI<23,4 (n=114)			
ADRB2					
C	109	172	0.597	1.145	0.694-1.888
G	31	56		0.874	0.530-1.440
C/C	43	63	0.580	1.00	
C/G	23	46		1.365	0.725-2.571
G/G	4	5		0.853	0.217-3.360
LPL					
Alleles and genotypes	**Allele and genotype frequency**		**p**	**CI**	**95%OR**
	BMI> 23,5 (n=70)	BMI<23,4 (n=114)			
C	97	158	0.998	0.999	0.633-1.577
G	43	70		1.001	0.634-1.579
C/C	29	54	0.141	1.00	
C/G	39	50		0.689	0.372-1.274
G/G	2	10		2.685	0.551-13.087

Table 3. Data on biochemical parameters in apoA1 groups

Parameter	All (n=182) Me; Q1-Q3	ApoA1≤1.09 (n=50) Me; Q1-Q3	ApoA1>1.09 (n=132) Me; Q1-Q3	P value
TC *(mmol/l)	4.37; 3.61-4.81	4.01; 3.46-4.54	4.16; 3.71-4.91	0.159*
HDL (mmol/l)	0.66; 0.24-0.99	0.08; 0.37-0.51	0.42; 0.02-1.23	0.018
LDL (mmol/l)	1.85; 1.37-2.16	1.90; 1.47-2.18	1.91; 1.29-2.16	0.230
TRG (mmol/l)	1.47; 1.24-1.71	1.42; 1.23-1.59	1.50; 1.23-1.72	0.173
Glucose (mmol/l)	5.18; 4.33-5.88	4.96; 4.54-5.59	5.0; 4.20-4.90	0.977
Insulin (SI/ml)	9.26; 3.4-12.55	4.25; 2.7-5.95	7.10; 3.7-13.9	0.001
HOMA_IR	2.21; 0.67-2.71	1.09; 0.62-1.45	1.64; 0.82-3.05	0.001
ApoB (g/l)	0.58; 0.49-0.67	0.86; 0.47-0.62	0.58; 0.5-0.68	0.030

** - statistical significance. **TC – total cholesterol, HDL – high density lipoprotein, LDL – very low density lipoprotein, TRG – triglycerides, ApoB – apolipoprotein B*

When comparing the average values of biochemical parameters by sex, the difference in average values was found only in apoA1 (p=0.008), and in other indicators, such as TC, HDL, LDL, TRG, glucose, insulin, IR, ApoB, there was no difference between the sex.

When considering the mean values of biochemical parameters between the apoA1 groups, the difference in mean values was revealed in the levels of HDL, insulin, insulin resistance index and apoB. For the rest of the biochemical parameters, no difference in mean values between the apoA1 groups was found (Table 3).

When conducting multivariate logistic regression, it was found that the G allele of the rs328 polymorphism of the *LPL* gene reduced the risk of developing A1 hypoapolipoproteinemia compared to the C allele, and when studying multivariate logistic regression between the *ADRB2* gene rs1042714 polymorphism and apoA1 groups, no relationship was found (table 4). It was also found that the dominant model of rs328 polymorphism of the *LPL* gene is associated with a low risk of A1 hypoapolipoproteinemia. The C/G and G/G genotypes reduce the risk of developing hypoapolipoproteinemia A1 by 0.22 and 0.46 times, respectively, compared with the C/C genotype. Also, the dominant model of rs328 polymorphism of the *LPL* gene showed that the C/G + G/G genotypes reduce the risk of A1 hypoapolipoproteinemia by 0.24 times. In turn, the heterozygous variant C/G reduces the risk of developing hypoapolipoproteinemia A1 by 0.24times compared with the homozygous C/C + G/G.

When studying the *LPL* gene and apoA1 groups, we found that the risk of hypoapoproteinemia A1 was associated with the rs328 polymorphism of the *LPL* gene (p = 0.002) and the odds ratio for the C/G genotype was 0.22 (CI 0.10-0.46), and for the G/G - 0.46 (CI 0.11-0.96), and when studying the relationship of the *ADRB2* gene with apoA1 groups, no relationship was found (p = 0.257).

In the present study, low levels of apoA1 were more common in girls compared with boys. Also, a statistically significant in-

Table 4. The relationship of rs328 and rs1042714 with apoA1 groups (n=184)

Model	Genotype	ApoA1≤1.09 (n=50)	ApoA1>1.09 (n=132)	OR (95% CI)	P-value	AIC	BIC
Codominant	C/C	11 (22%)	72 (54,5%)	1.00	2e-04	202,4	212.1
	C/G	36 (72%)	51 (38,6%)	**0.22 (0.10-0.46)**			
	G/G	3 (6%)	9 (6,8%)	**0.46 (0.11-1,96)**			
Dominant	C/C	11 (22%)	72 (54,5%)	1.00	1e-04	201,7	208.1
	C/G-G/G	39 (78%)	60 (45,5%)	**0.24 (0.11-0.50)**			
Recessive	C/C-C/G	47 (94%)	123 (93,2%)	1.00	0.84	218	224,4
	G/G	3 (6%)	9 (6,8%)	1,15 (0.30-4,42)			
Overdominant	C/C-G/G	14 (28%)	81 (61,4%)	1.00	<0.0001	201,5	207,9
	C/G	36 (72%)	51 (38,6%)	**0.24 (0.12-0.50)**			
Log-additive	---	---	---	**0.42 (0.24-0.74)**	0.0018	208,8	214,6
Relationship between rs1042714 and apoA1 groups (n=184)							
Codominant	C/C	31 (62%)	73 (55,3%)	1.00	0.26	215.7	225.4
	C/G	15 (30%)	54 (40.9%)	1.53 (0.75-3.11)			
	G/G	4 (8%)	5 (3.8%)	0.53 (0.13-2,11)			
Dominant	C/C	31 (62%)	73 (55,3%)	1.00	0.41	215.2	221.6
	C/G-G/G	19 (38%)	59 (44,7%)	1.32 (0.68-2.57)			
Recessive	C/C-C/G	46 (92%)	127 (96.2%)	1.00	0.26	213.7	220.2
	G/G	4 (8%)	5 (3.8%)	0.45 (0.12-1.76)			
Overdominant	C/C-G/G	35 (70%)	78 (59,1%)	1.00	0.17	215.1	221.5
	C/G	15 (30%)	54 (40,9%)	1.62 (0.80-3.24)			
Log-additive	---	---	---	1.07 (0.62-1.87)	0.8	214.8	221.2

crease in BMI was more common in boys compared with girls. We found that apoA1 levels were associated with HDL, insulin, insulin resistance index, and apoB. Low apoA1 levels were more common in adolescents with low HDL cholesterol and elevated levels of insulin, insulin resistance index and apoB, which is consistent with other studies.In studies conducted in the Chinese population, serum levels of HDL-C and ApoA1 were higher in women than in men, they also did not have a significant diffe - ence in the levels of TC, TRG, LDL-C and ApoA1 with ApoB between the two sexes [13]. Freitas et al. in a study among obese adolescents, plasma LDL and VLDL were higher in girls than in boys and were independently associated with multiple lipid markers, while increased LDL was influenced by gender, age, puberty, BMI and waist size in adolescents with obesity [14].

We found that the rs328 polymorphism of the *LPL* gene is associated with the risk of A1 hypoapolipoproteinemia in adolescents in the Kazakh population and the G allele reduces the risk of A1 hypoapolipoproteinemia by 0.42 times compared with the C. Bänsch et al. investigated basal levels of growth hormone in blood serum, which positively correlated with triglycerides, HDL, apoA-I and apoA-II and negatively with *LPL* activity [15]. Wood A.C. and et al provide evidence that the minor allele of variant *LPL* S447X is associated with large VLDL diameters in groups defined by the lipoprotein diameter pattern, which includes small particles of LDL and HDL [16].

We also found that the heterozygous C/G genotype of the rs328 polymorphism of the *LPL* gene reduced the risk of developing A1hypoapolipoproteinemia by 0.24 times compared with the homozygous C/C+G/G genotypes. The C/G genotype of rs328 polymorphism of the *LPL* gene reduced the risk of developing A1 hypoapolipoproteinemia by 0.22, and the G/G genotype by 0.46 times, and the C/G+G/G genotypes reduced the risk of developing A1 hypoapolipoproteinemia by 0.24 times. In studies by Wood A.C et al. the genetic variant of GG (rs328) in European populations is associated with low levels of triglycerides and low density lipoproteins [16]. Radha et al. investigated the relationship of SNP T93G and G53C of the *LPL* gene among Asian Indians with obesity and type 2 diabetes and concluded that SNP G53C protects both from obesity and type 2 diabetes, and SNP T93G is associated only with obesity [17].

Ishiyama-Shigemoto S. et al. conducted a study of the Japanese population among obese individuals and found a higher frequency of the G/G Gln27Glu genotype in obese individuals compared to thin [18]. Ochoa et al. found in girls of carriers of the G allele an increased risk of obesity, but they also did not find any connection between Gln27Glu polymorphism and obesity in boys [19]. Chou Y-C. et al. conducted a study in Taiwan of Arg16Gly and Gly27Gly polymorphisms of the *ADRB2* gene among adolescents with obesity and revealed a reliable association of Arg16Gly polymorphism with obesity in adolescent girls, and individuals with the Gly/Gly genotype had a lower chance of obesity [20]. In our study, the rs1042714 polymorphism of the *ADRB2* gene was not associated with the risk of A1 hypoapolipoproteinemia.

Conclusions. This study showed that the rs328 polymorphism of the *LPL* gene and the rs1042714 polymorphism of the *ADRB2* gene are not associated with the risk of obesity among adolescents of Kazakh nationality. The study revealed that the rs328 polymorphism of the *LPL* gene is associated with a risk of A1 hypoapolipoproteinemia in adolescents of Kazakh nationality. It was found that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of developing A1 hypoapolipo-

proteinemia in adolescents of the Kazakh population, while the rs1042714 polymorphism of the *ADRB2* gene is not associated with the risk of A1 hypoapolipoproteinemia. It was also revealed that with a low level of apoA1, high levels of insulin, insulin resistance index and apoB and low levels of HDL are more common, which can contribute to the development of dyslipidemia, obesity and cardiovascular complications in the future. High BMI was more common among Kazakh boys compared to Kazakh girls.

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SUMMARY

LPL AND ADRB2 GENE POLYMORPHISMS: RELATIONSHIP WITH LIPIDS AND OBESITY IN KAZAKH ADOLESCENTS

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The study is aimed at studying the relationship of polymorphisms of the *ADRB2* (rs1042714) and *LPL* (rs328) genes with lipid changes and weight gain in adolescents of Kazakh nationality.

A total of 184 Kazakh adolescents, aged 15 to 18, were included in the study. The main group included 70 overweight adolescents (BMI>23.5), and the control group included 114 adolescents with normal physique (BMI≤23.4).

Single nucleotide polymorphisms rs1042714 [C/G] and rs328

[C/G] were determined by the TaqMan method, using for genotyping the DNA of peripheral blood cells.

When comparing the polymorphisms rs1042714 of the *ADRB2* gene (p=0.58) and rs328 of the *LPL* gene (p=0.12) with a body mass index, no relationship was found. The results of the study show that A1 hypoapolipoproteinemia was associated with the rs328 polymorphism of the *LPL* gene (p=0.002). rs1042714 of the *ADRB2* gene is not associated with apoA1 groups (p=0.257). A comparison of body mass index (BMI) by gender showed that boys had a significantly higher BMI compared to girls (p=0.002). Between polymorphisms rs328 and rs1042714 did not reveal a statistically significant relationship with the risk of obesity among adolescents of Kazakh nationality. The rs328 polymorphism has an association with A1 hypoapolipoproteinemia in adolescents of Kazakh nationality. rs1042714 of the *ADRB2* gene is not associated with a risk of A1hypoapolipoproteinemia.Low levels of apoA1 are more often accompanied by low levels of HDL (High-Density Lipoprotein) and high levels of insulin, insulin resistance index and apoB.

Keywords: LPL, ADRB2, obesity, adolescents, BMI, A1 apolipoprotein.

РЕЗЮМЕ

ПОЛИМОРФИЗМЫ ГЕНОВ LPL И ADRB2: ВЗАИМОСВЯЗЬ С ЛИПИДАМИ И ОЖИРЕНИЕМ У КАЗАХСКИХ ПОДРОСТКОВ

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Исследована связь полиморфизмов генов ADRB2 (rs1042714) и LPL (rs328) с изменениями липидов и ростом массы тела у подростков казахской национальности.

Наблюдались 184 казахских подростков в возрасте от 15 до 18 лет. Основную группу составили 70 подростков с избыточной массой тела (ИМТ>23,5), контрольную грппу - 114 подростков с нормальным телосложением (ИМТ≤23,4). Однонуклеотидные полиморфизмы rs1042714 [C/G] и rs328 [C/G] определяли методом TaqMan, используя для генотипирования ДНК клеток периферической крови.

Сравнение полиморфизмов rs1042714 гена ADRB2 (p=0,58) и rs328 гена LPL (p=0,12) с индексом массы тела связи не выявило. Результаты исследования показали, что гипоаполипопротеинемия А1 связана с полиморфизмом rs328 гена LPL (p=0.002). rs1042714 гена ADRB2 не ассоциируется с группами апоА1 (p=0.257). Сравнение ИМТ по полу продемонстрировало, что у подростков мужского пола показатель ИМТ значимо выше в сравнении с женским полом (p=0.002). Между полиморфизмами rs328 и rs1042714 статистически значимой связи с риском развития ожирения среди подростков казахской национальности не выявлено. Полиморфизм rs328 ассоциируется с гипоаполипопротеинемией А1 у подростков казахской национальности, тогда как rs1042714 гена ADRB2 не связан. Низкий уровень аполипопротеина А1 чаще сопровождается низким уровнем липопротеинов высокой плотности и высоким уровнем инсулина, индекса инсулинорезистентности и аполипопротеина В.

რეზიუმე

LPL და ADRB2 გენების პოლიმორფიზმი: ურთიერთობა ლიპიდებთან და სიმსუქნე ყაზახ მოზარდებში

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კვლევის მიზანს წარმოადგენს ADRB2 (rs1042714) და LPL (rs328) გენების პოლიმორფიზმის დამოკიდებულების შესწავლა ლიპიდურ ცვლილებებთან და წონის მატებასთან ყაზახი ეროვნების მოზარდებში.

კვლევაში მონაწილეობდა 15-დან 18 წლამდე 184 მოზარდი. ძირითად ჯგუფში შედიოდა 70 მოზარდი ჭარბი წონით (BMI>23,5), საკონტროლო ჯგუფში - 114 მოზარდი ნორმალური წონით (BMI≤23,4). ერთჯერადი ნუკლეოტიდის პოლიმორფიზმი rs1042714 [C/G] და rs328 [C/G] განისაზღვრა TaqMan მეთოდით, დნმ-ის გამოყენებით პერიფერიული სისხლის უჯრედების გენოტიპებისათვის. ADRB2 გენის rs1042714 პოლიმორფიზმის და LPL გენის rs328 (p=0.12) პოლიმორფიზმების შედარებისას სხეულის მასის ინდექსთან კავშირი არ გამოვლინდა. კვლევის შედეგები აჩვენებს, რომ A1 ჰიპოაპოლიპოპროტეინემია ასოცირდება LPL გენის rs328 პოლიმორფიზმთან (p=0.002), ხოლო ADRB2 გენის rs1042714 არ ასოცირდება აპო 1 ჯგუფებთან (p=0.257). BMI–ს შედარებამ სქესის მიხედვით აჩვენა, რომ BMI ბიჭებში მნიშვნელოვნად მაღალი იყო გოგონებთან შედარებით (p=0.002).

rs328 და rs1042714 პოლიმორფიზმებს შორის სტატისტიკურად მნიშვნელოვანი კავშირი არ არსებობდა ყაზახური ეროვნების მოზარდებში სიმსუქნის რისკთან. Rs328 პოლიმორფიზმი ასოცირდება A1 ჰიპოაპოლიპოპროტეინემიასთან ყაზახური ეროვნების მოზარდებში. ADRB2 გენის rs1042714 არ ასოცირდება A1 ჰიპოაპოლიპოპროტეინემიის განვითარების რისკთან. ApoA1-ის დაბალ დონეს უფრო ხშირად თან ახლავს HDL-ის დაბალი დონე და ინსულინის მაღალი დონე, ინსულინის წინააღმდეგობის ინდექსი და apoB.

ВЛИЯНИЕ АЛКОГОЛИЗМА И АЛКОГОЛЬНОЙ ЗАВИСИМОСТИ НА ПОВЫШЕНИЕ УРОВНЯ ПРЕСТУПНОСТИ В ОБЩЕСТВЕ (МЕДИКО-ПРАВОВЫЕ МЕРЫ ПРОФИЛАКТИКИ)

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Алкоголизм – сложные социальные явления. Об их сложности и многогранности свидетельствует факт устойчивой склонности к алкоголю самых разных социальных слоев и профессиональных групп населения, людей различного социального положения, материального достатка, уровня образования, возраста и пола. Алкоголизм имеет медицинские и социальные последствия как для лица, его потребляющего, так и для окружения: повышает риск ухудшения здоровья, ставит под угрозу развитие отдельного индивида и общества в целом [2].

Именно на этих явлениях базируется и алкоголизация населения, поскольку алкоголизация – это процесс, который происходит в обществе вследствие роста пьянства и алкоголизма и объясняется тем, что на современном этапе в обществе происходят негативные процессы, которые в итоге приводят к стремительному развитию алкоголизма и наркомании [17].

Алкоголизация давно не является проблемой каждого отдельно взятого государства. Современные глобализационные мировые процессы способствуют созданию единого пространства во всех сферах жизнедеятельности, в том числе и в социокультурной, что, в свою очередь, способствует алкоголизации отдельных индивидов и общества в целом [1]. Как правило, статистические данные стран, в которых высокие показатели потребления алкогольных напитков, базируются исключительно на официальных данных. Анализ проводимых на сегодняшний день социологических исследований позволяет констатировать, что тенденции развития и распространения алкоголизма, а также ускорение процессов алкоголизации населения не зависят от уровня жизни. Согласно данным одного из таких исследований [4], к шести странам с чрезмерным употреблением алкогольных напитков относятся Индия (41 раз в год), Дания (41 раз в год), Австралия (47 раз в год), Канада (48 раз в год) США (50 раз в год), Великобритания (51 раз в год). Имеется также другая информация, в частности, приводится совершенно иная статистика по наиболее алкоголизированным странам (за основу берется количество алкоголя per capita, который используется в год), в десятку таких стран входят Словакия (13 литров), Чехия (13 литров), Венгрия (13,3 литров), Андорра (13,8 литров), Украина (13,9 литров), Румыния (14,4 литров), Россия (15,1 литров), Литва (15,4 литров), Молдова (16,8 литров), Беларусь (17,5 литров) [6].

Общеизвестно, что алкоголизация является девиантным процессом, который характеризуется определенной динамикой, как в отдельных странах, так и в мире [14]. Злоупотребление алкоголем является достаточно распространенным и устойчивым фактором риска в США, где это явление (наряду с наркоманией) считается преступной деятельностью, способствует совершению более тяжких преступлений [22]. Особую опасность представляет этот процесс для несовершеннолетних, в силу их возрастной уязвимости, неустойчивости психики, что способствует развитию алкоголизма, табакокурения и наркомании среди этой категории населения [20].

Распространение алкоголизма непосредственно связано с повышением уровня преступности в обществе, что доказывается исследованием влияния алкогольной зависимости на преступность [16]. Алкогольное опьянение является причиной практически почти всех насильственных преступлений [10]. Алкоголизация напрямую связана с преступностью и в самом пьянстве генетически заложена его общественно опасная направленность, что подтверждается увеличением преступности среди лиц, достигших 21-летнего возраста, прямопропорционально увеличивается преступность [12]. Лица, достигшие указанного возраста на 5,9% чаще совершают преступления, что объясняется разрешением употребления алкоголя [7]. Чрезмерное потребление алкоголя способствует общественному неповиновению, антисоциальному поведению, совершению бытовых, межличностных и сексуальных насильственных действий [9], а также насилию с применением огнестрельного оружия [21,23].

Следовательно, алкоголизм, который является основой процесса алкоголизации, негативно влияет не только на жизнь отдельного лица, непосредственно употребляющего алкоголь, но является также общесоциальной проблемой, поскольку нарушает порядок во всех сферах общественной жизни. Это порождает ряд проблем, которые выходят за пределы одной страны, в частности в экономической и правоохранительной сферах, сфере здравоохранения и обеспечения нормального физического, психического и нравственного развития несовершеннолетних.

Приведенные выше исследования, проводимые в сфере противодействия алкоголизации населения, рекомендации по применению конкретных мер профилактики алкоголизма на национальном и международном уровнях доказывают актуальность разработки эффективных мер медико-правовой профилактики на уровне национальной и международной антиалкогольной политики.

Негативное влияние алкоголизации населения на все сферы общественной жизни диктует необходимость выработки наиболее универсальных и действенных способов воздействия на чрезмерно употребляющих алкогольные напитки, а также регулярно употребляющих алкоголь для замедления процесса алкоголизации и снижения уровня алкоголизма.

Цель исследования – определить универсальные медико-правовые меры индивидуальной и общегосударственной профилактики алкоголизации населения путем разработки и принятия международного нормативно-правового акта – Конвенции о борьбе с алкоголизацией общества.

Основной задачей государств-участников Конвенции является на основе международных стандартов, содержащихся в этом документе, внести изменения в свои национальные нормативно-правовые акты для обеспечения эффективности мер профилактики и лечения алкоголизма.

Материал и методы. Авторами статьи применены методы сравнения, сопоставления, логического анализа, статистический метод и метод анкетирования.

Статистический метод применялся с целью анализа данных официальной статистики за 2014-2019 гг. по совершенным несовершеннолетними в состоянии алкогольного опьянения преступлениям, их видам и количеству (Таблица 1) [21]. Метод сопоставления применялся при сравнении данных по изучению развития аддиктивного поведения у подростков вследствие употребления алкоголя (на примере Кольского полуострова) за 2013-2017 гг., в котором участвовали 539 респондентов 15-летнего возраста [15]; а также при изучении влияния специальных программ, разработанных для противодействия алкоголизму и его развитию: программа, разработанная в США «Трезвость 24/7», которая проводилась в 2005-2011 гг. с участием 16 932 лиц [13]. Методы сравнения и логического анализа применялись при сравнении норм уголовного законодательства четырнадцати стран в рамках установления эффективности уголовно-правовых мер противодействия алкоголизации населения (Таблица 2). Метод анкетирования использовали при опросе 1390 студентов высших учебных заведений (г. Черкассы, Украина) с целью выявления факторов, влияющих на распространение употребления алкоголя среди молодежи.

Таблица 1. Преступления, совершенные в состоянии алкогольного опьянения (на примере Украины)

Год	Общее количество осужденных за совершение преступлений	Количество осужденных за преступления, совершенные в состоянии алкогольного опьянения	Виды преступлений	Количество осужденных несовершеннолетних, совершивших преступление в состоянии алкогольного опьянения
2014	102170	20698	Преступления небольшой тяжести – 4010 Преступления средней тяжести – 8259 Тяжкие – 7539 Особо тяжкие – 890	Всего преступлений – 527 Из них: тяжкие – 304 особо тяжкие – 25
2015	94798	14908	Преступления небольшой тяжести – 2370 Преступления средней тяжести – 5772 Тяжкие – 6068 Особо тяжкие – 698	Всего преступлений – 368 Из них: тяжкие – 222 особо тяжкие – 20
2016	76217	11143	Преступления небольшой тяжести – 1732 Преступления средней тяжести – 4336 Тяжкие – 4554 Особо тяжкие – 521	Всего преступлений – 229 Из них: тяжкие – 150 особо тяжкие – 12
2017	76804	9318	Преступления небольшой тяжести – 1483 Преступления средней тяжести – 3610 Тяжкие – 3774 Особо тяжкие – 451	Всего преступлений – 165 Из них: тяжкие – 92 особо тяжкие – 14
2018	73659	7142	Преступления небольшой тяжкости – 1192 Преступления средней тяжести – 2941 Тяжкие – 2675 Особо тяжкие – 334	Всего преступлений – 121 Из них: тяжкие – 67 особо тяжкие – 7
2019	70375	6518	Преступления небольшой тяжести – 1186 Преступления средней тяжести – 2643 Тяжкие – 2377 Особо тяжкие – 312	Всего преступлений – 108 Из них: тяжкие – 61 особо тяжкие – 7

Результаты и обсуждение. Алкоголизм, который является основой процесса алкоголизации – это явление, лежащее в плоскости различных сфер регулирования жизнедеятельности (сфера здравоохранения, экономическая, социальная, уголовно-правовая, ювенальная). Алкоголизм также тесно связан с преступностью, является одним из факторов, неотъемлемо сопровождающих совершение определенных видов преступлений. Об этом свидетельствуют данные официальной статистики по Украине за 2014-2019 годы (Таблица 1) [3].

Анализ приведенных данных свидетельствует, что меры предотвращения алкоголизма как явления требуют совместных усилий отдельных направлений государственной политики. При этом необходимо понимать причины и способы возникновения и распространения случаев алкоголизма с целью их предотвращения. Причинами частого и нерегулируемого потребления алкоголя являются: нарушение нормального физического, психологического и нравственного развития несовершеннолетних; недостаточность воспитания со стороны родителей (опекунов), общий низкий уровень культуры в обществе, психологическая неустойчивость характера членов общества.

Существуют также факторы, которые оказывают непосредственное влияние на рост уровня алкогольной зависимости среди различных слоев населения, в том числе и среди несовершеннолетних. Прежде всего, это состояние общества и существующие проблемы в сферах государственного регулирования: проблемы экономического характера, обусловливающие тяжелое экономическое положение населения; несовершенство сферы социальной защиты наиболее уязвимых слоев населения; относительная неконтролируемость выпуска и продажи алкогольных напитков со стороны государства и игнорирование проблемы нелегального изготовления и продажи алкогольных напитков; культурный и правовой нигилизм как среди взрослых, так и среди несовершеннолетних членов общества, преодоление которого не является приоритетным направлением государственной политики.

На рост уровня алкоголизма в обществе наиболее значимое влияние имеют факторы, относящиеся преимущественно к социально-бытовой сфере: игнорирование симптомов алкоголизма у себя или у близких/родственников ввиду отсутствия или недостаточной осведомленности о признаках и пагубности алкоголизма для здоровья отдельного человека и общества в целом; несовершенство пропаганды в сфере здорового образа жизни; общественные традиции по употреблению алкогольных напитков, свойственные отдельно взятым регионам или странам; поощрения к употреблению алкогольных напитков среди населения (политика отдельных обществ или торговых заведений, акционные скидки на алкоголь, выдача разрешений на открытие торговых точек по продаже дешевых некачественных и общедоступных алкогольных напитков); распространенное явление потребления алкоголя на рабочих местах и производстве; неотлаженность социальной работы индивидуальной направленности с лицами, склонными к систематическому потреблению алкоголя.

Алкоголизация населения в последние годы имеет тенденцию к омоложению – все больше лиц в возрасте до 21 года приобщаются к алкоголю. Проблема алкоголизации несовершеннолетних существует и в странах арабского мира: в результате проведенного в Ливане исследования детерминант потребления алкоголя молодежью разрабатаны рекомендации по уменьшению употребления алкогольных напитков [8]. Алкоголизм несовершеннолетних распространен и в Арктическом регионе. В одном из исследований с участием 539 респондентов на примере Кольского полуострова изучалось развитие аддиктивного поведения у подростков вследствие потребления алкоголя. В результате установлено, что подростки с алкогольной зависимостью имели проблемы с соматическим и психическим здоровьем, а их психическое состояние влияло на поведение в целом [15]. В этом исследовании определены наиболее эффективные социальные меры противодействия и борьбы с алкоголизацией как на национальном, так и международном уровне.

Авторами статьи проведено анкетирование студентов высших учебных заведений (г. Черкассы, Украина) с целью выявления наиболее значимых факторов, способствующих употреблению алкогольных напитков среди молодежи. Опрошено 1390 респондентов, среди которых 560 (40%) были мужского и 830 (60%) женского пола в возрасте от 17 до 23 лет. В ходе обработки информации выявлены закономерности, касающиеся потребления молодежью алкогольных напитков, в частности 370 (27%) опрошенных употребляют алкоголь 1 раз в неделю, соотношение лиц мужского и женского пола - 40%/60%, соответственно. Из них 190 респондентов склонны к потреблению алкоголя в сложных жизненных ситуациях, большинство потребляет пиво, слабоалкогольные напитки, реже – крепкие; 90 (25%) из 370 респондентов работают, из них 40 – в ресторанах или кафе; алкогольные напитки этими лицами употребляются преимущественно на вечеринках и дома; за сентябрь 2020 года 320 (87,5%) находились в состоянии алкогольного опьянения от 1 до 4 раз, все они впервые почувствовали себя нетрезвыми в возрасте от 15 до 18 лет. Что касается семейно-бытовых условий, чаще всего употребляющие алкоголь являются имеют средний уровень материального обеспечения семьи; 280 (76%) из 370 проживают с родителями; у 270 (73%) из 370 оба или один из родителей со средним специальным образованием, у остальных – оба родителя с высшим образованием.

Факторами, которые больше всего повлияли на склонность опрошенных студентов к потреблению алкогольных напитков, являются: только со 180 (49%) из 370 студентов родителями проводились беседы о вреде употребления алкоголя; 230 (63%) родители предлагали потреблять алкоголь дома. Следовательно, основными факторами, оказывающими наибольшее влияние на склонность студентов к потреблению алкоголя, являются: недостаточность профилактической работы с ними со стороны родителей, склонение к потреблению алкогольных напитков самими родителями, уровень образования родителей и особенности психо-эмоциональных состояние респондентов.

С елью полного охвата всех факторов и причин систематического и чрезмерного потребления алкоголя в пределах противодействия этому явлению, необходимо выработать комплекс профилактических мер. Именно это и обусловило принятие Глобальной стратегии сокращения вредного потребления алкоголя Всемирной Организацией Здравоохранения (далее – ВОЗ) в 2010 году [2].

Игнорирование любого из существующих в обществе факторов, влияющих на алкоголизацию населения, приводит к снижению эффективности всего комплекса применяемых мер. Однако при осуществлении эффективного профилактического воздействия на факторы алкоголизации населения, особенного на первичном (индивидуальном) уровне, причины автоматически устраняются.

Значительное влияние на формирование личности осуществляется через семью, школу или другие учебные заведения, круг общения. Если в этих средах на подростков, прежде всего несовершеннолетних, оказывается негативное влияние, пропагандируется или не возбраняется (не критикуется) употребление алкогольных напитков, то это способствует алкоголизации. Основными средствами противодействия алкоголизации таких лиц в медико-социальной сфере является доступ к приемлемым по цене и эффективности службам профилактики и оказания первой помощи. В отношении несовершеннолетних и малолетних лиц, не желающих принимать алкоголь, но находящихся в условиях риска, необходимо в рамках медицинского права разработать меры защиты и поддержки трезвого образа жизни. При этом государственная политика в сфере здравоохранения должна быть направлена на разработку и координацию стратегических направлений профилактики и оказания необходимой помощи, а также обеспечение общедоступности таких средств для лиц с низким социально-экономическим статусом (ст. 12, 21 Глобальной стратегии) [2], способствуя тем самым уменьшению потребления алкоголя среди молодежи.

К мерам противодействия алкоголизации населения должно быть приобщено медицинское направление. В рамках этих специальных мер ведущую роль играют Министерства здравоохранения отдельных стран, которые обеспечивают взаимодействие других министерств и сторон, заинтересованных в выработке эффективных мер противодействия алкоголизму, в частности в обеспечении специальных лечебных и профилактических стратегий (ст. 15, 19, 20, 46, 47, 52 Глобальной стратегии) [2].

Для реализации поставленной задачи необходима информационная основа, базирующаяся на конкретных статистических данных, содержащих сведения о проблемах, вызванных чрезмерным потреблением алкоголя, возможные меры по его сокращению. Для этого целесообразно осуществлять мониторинг количества потребления алкоголя в разных странах и анализ информации о вреде чрезмерного потребления; влияния алкоголизма на экономическое и социальное положение как отдельно взятой личности, так и общества в целом, особенно в отношении стран с самым высоким уровнем алкоголизации. Предоставление такого рода информации должны обеспечивать специализированные организации или агентства, которые обязаны осуществлять такую деятельность на внутригосударственном и международном уровнях путем разработки специальных информационных ресурсов (интернет-сайты, периодические издания, справочники). Осуществление такой деятельности предусмотрено в указанной Глобальной стратегии сокращения вредного потребления алкоголя. Любая медицинская информация не должна запугивать, а только объяснять, почему потребление алкоголя вредно и как с ним бороться.

С учетом вышеизложенного, в рамках стратегий антиалкогольного направления, и руководствуясь рекомендациями ВОЗ службы здравоохранения отдельных стран должны создаваться специальные социальные программы. Цель программ – предупредить как со стороны медицинских, так и социальных работников, процесс алкоголизации молодежи, остановить его среди лиц, систематически потребляющих алкоголь, но не осознающих опасности этого. В результате действия таких программ произойдет ранняя профилактика алкоголизма, скрининг и ресоциализация алкозависимых лиц на уровне первичной медико-санитарной помощи [2].

В США разработана и действовует специальная программа касательно правонарушителей, совершивших преступления в состоянии алкогольного опьянения, которая предусматривает введение трезвости 24/7 на определенных территориях. В ней с 2005 по 2011 гг. участвовали 16932 лиц. Для изучения влияния этой программы сопоставлены данные по годам, начиная с момента её введения. Анализ полученных данных в результате действия программы «Трезвость 24/7» показал, что она положительно повлияла на оздоровление населения: в период её действия значительно уменьшилась смертность [13].

Основным направлением программ должна быть реализация системного исправительно-психического воздействия, т.е. укрепление психики уязвимых лиц, развитие у них устойчивости к потреблению алкоголя. Большое значение имеет ориентировать население на безалкогольный образ жизни. Изменение отношения к алкогольным напиткам должно сопровождаться приобретением навыков решать жизненные проблемы без алкоголя и наличием альтернативы (мотивация). Исправительно-социальные меры противодействия в этих программах должны направляться на смену неправильных установок отдельных личностей.

В контексте исследования значимым является вопрос об индивидуальных мерах ранней профилактики. Считаем, что для его успешного разрешения необходимо разработать определенный алгоритм выявления потенциальных алкоголиков, в котором будут использованы психологические и медицинские критерии. Следует выявить наиболее характерные психобиологические характеристики лиц, систематически употребляющих алкоголь или уже болеющих алкоголизмом, и сформировать их четкий перечень. Выявление комплекса таких характеристик у несовершеннолетних и применение к ним указанных выше мер профилактики снизит риск развития алкоголизма. Не исключено применение новейших достижений науки и техники, в частности интересным является предложение по применению нового исследовательского подхода к сфере ранней профилактики алкоголизма: эффективным и целесообразным средством является применение электроэнцефалографических методов для выявления генетической предрасположенности к употреблению алкоголя и осуществление культурно-воспитательного, психо-социального воздействия на индивидов, находящихся в зоне риска [8].

Судя о поощрительных и медико-социальных профилактических мерах по преодолению алкоголизма, следует упомянуть о необходимости использования запрещающих мер воздействия. В большинстве случаев они менее эффективны (часто вызывают желание поступать вопреки запретам), однако без них нельзя оказывать комплексное замедляющее воздействие на процесс алкоголизации населения: индивидуальные и социально-экономические меры, направленные на лица, склонные к алкоголизму. Речь идет об уголовно-правовых мерах, которые должны быть не только карающего, но и принудительного характера. Уголовное законодательство, как правило, содержит нормы, обязывающие лицо, совершившее преступление, не употреблять алкогольные напитки и наркотические средства или подвергнуться мерам медицинского характера (Таблица 2).

Следует обратить внимание на предписания норм уголовного законодательства ряда стран, которые предусматривают обязательное согласие на прохождение курса лечения от алкоголизма (указанное согласие может быть только в том случае, если лицо является правоспособным, поскольку в случае, если оно не будет осознавать свои действия и не может руководить ими, то не сможет адекватно оценить свое состояние и необходимость лечения).

Таблица 2. Нормы уголовного законодательства в сфере борьбы с алкоголизмом

Страна	Номер статьи (нормы) Уголовного кодекса	Содержание нормы
Дания	ст. 57	Обязательство воздерживаться от злоупотребления алкоголем или употребления наркотических веществ
Норвегия	п. «c» ч. 3 § 53 п. «e» ч. 3 § 53	Обязательство не употреблять алкогольные напитки и наркотические вещества Обязательство прохождения осужденным антиалкогольной пропаганды
Республика Сербия	ст. 73	Обязательство не употреблять алкогольные напитки и наркотические вещества
Эстонская Республика	ст. 75	Обязательство не употреблять алкогольные напитки и наркотические вещества
Республика Беларусь	ч. 5 ст. 90, ч. 4 ст. 77	Обязательство пройти соответствующий курс лечения от алкоголизма в специальном заведении
Австрия	п. 2 абз.2 § 51	Обязательство не употреблять алкогольные напитки
Швейцария	ч. 2 ст. 41	Обязательство не употреблять алкогольные напитки
Венгрия	ст. 70	Принудительная забота об алкоголиках
Республики Молдова	ст. 103	Установление опеки над хроническим алкоголиком и наркоманом
Румыния	ч. 3 ст. 103	Обязанность поддаться средствам контроля, тритмента или заботы с целью остановки интоксикации
Федерация Боснии и Герцеговины	ч. 3 ст. 61	Обязательный медицинский тритмент алкоголиков и наркоманов
Украина	п. 5 ч. 2 ст. 76	Обязательство пройти курс лечения от алкоголизма
Грузия	ст. 65	при условном осуждении и наличии оснований для этого обязанность пройти курс лечения от алкоголизма

Предложения по разработке конкретных эффективных мер противодействия алкоголизации населения на международном уровне и на уровне отдельных стран, которые могут быть применены практически каждым государством, высказываются в современных исследованиях в различных областях: в сфере здравоохранения, юриспруденции, менеджмента, медицины, промышленности.

Необходимо отметить безрезультатность и неэффективность определенных усилий по сокращению чрезмерного потребления алкогольных напитков. К таким мерам относится антиалкогольная политика, направленная на ограничение доступа к алкоголю [11] или противодействие распространению алкоголизма путем повышения минимальных цен на алкоголь [5,19,38]. Однако повышение официальных цен на алкоголь (особенно в бедных странах и регионах) способствует увеличению количества некачественных, изготовленных нелегально, алкогольных напитков. А наличие такой продукции, в свою очередь, приводит к стремительному ухудшению здоровья и даже повышению уровня смертности среди лиц, принимющих алкоголь.

Считаем, что в разработке специальных мер профилактики и противодействия распространению алкоголизма наиболее эффективной является тесное партнерство между государством и обществом. Именно такой подход может обеспечить наилучшие результаты.

Вышеприведенные данные позволяют сформулировать необходимые и действенные для профилактики алкоголизации населения меры. Основы медико-социальной профилактики алкоголизации населения закреплены в Глобальной стратегии сокращения вредного потребления алкоголя ВОЗ 2010 года. Однако нормы этой стратегии имеют рекомендательный характер и не являются обязательными для выполнения государствами-участниками. Поэтому рекомендуем органам здравоохранения государств – постоянным членам Совета Безопасности ООН, при участии ВОЗ разработать Конвенцию о борьбе с алкоголизацией общества, которая будет иметь обязательный характер. Предложенная Конвенция должна содержать международные стандарты борьбы с алкоголизацией, в частности международные стандарты создания медико-социальных нормативно-правовых актов государствами-участниками Конвенции для принятия эффективных мер профилактики и лечения алкоголизма на национальном уровне.

Органам здравоохранения будущих государств-участников указанной Конвенции предлагается разработать и принять на национальном уровне нормативно-правовой акт, в котором будут определены основные меры профилактики алкоголизации населения и лечения от алкоголизма. Документ должен включать: определение понятий «алкоголизация населения» и «алкоголизм»; меры профилактики алкоголизма медицинского характера (исследование психобиологических особенностей и определение общих признаков лиц, систематически употребляющих алкоголь, с целью ранней профилактики алкоголизма у несовершеннолетних лиц, имеющих аналогичные признаки; информацию об основных симптомах алкогольной зависимости и рекомендации по преодолению влечения к его потреблению (с ссылками на специальные справочные материалы медицинского характера); меры противодействия алкоголизму социально-педагогического характера со стороны образовательных, общественных и государственных организаций, т.е. проведение в образовательных учреждениях специальных лекций и бесед об опасности алкоголизма, вредности алкогольных

напитков, о культуре их потребления, обеспечении досуга наиболее уязвимых членов общества в целях расширения возможностей для физического, творческого, культурного развития, организация курсов или семинаров для родителей по обеспечению надлежащего физического, психического и нравственного развития несовершеннолетних); меры противодействия алкоголизму запрещающего и контролирующего характера: разработка и применение программ по ограничению доступа к алкоголю определенных категорий лиц, склонных к потреблению алкоголя или больных алкоголизмом, усиление государственного контроля над продажей и нелегальным производством алкогольных напитков; меры противодействия алкоголизму уголовно-правового характера: разработка уголовно-правовых норм обязательственного характера по выполнению предписаний законодательства о воздержании от употребления алкоголя лиц, совершающих или склонных к совершению преступлений в состоянии алкогольного опьянения; нормы, касающиеся соответствующих условий лечения и применения соответствующих лечебных мер к лицам, больных алкоголизмом; нормы по обеспечению всеобщего доступа к информационным ресурсам данных в сфере алкоголизации.

Для обеспечения эффективности указанных мер и их выполнения необходимо закрепление соответствующих положений в действующих и, при необходимости, разработка и введение в действие новых нормативно-правовых актов государств-участников. В национальное законодательство об образовании необходимо включить соответствующие положения о проведении образовательных и разъясняющих мер об опасности алкоголизма в пределах образовательных программ, об организации досуга несовершеннолетних, о работе с родителями несовершеннолетних, находящихся в зоне риска. В законодательстве об органах местного самоуправления следует предусмотреть проведение специальных мер для организации досуга и создания специальных центров реабилитации для лиц, прошедших лечение от алкоголизма. В законодательстве о внутренних правоохранительных органах включить нормы, содержащие четкие предписания по борьбе с нелегальной торговлей и нелегальным выпуском алкогольных напитков; по усилению контроля за соблюдением установленного порядка употребления алкогольных напитков. В национальном уголовном законодательстве следует регламентировать обязательства лиц, склонных к чрезмерному потреблению алкоголя и в состоянии алкогольного опьянения совершению уголовных правонарушений, не употреблять алкогольные напитки и пройти курс антиалкогольной пропаганды.

Предложенные меры являются универсальными для большинства стран, так как они направлены на снижение уровня алкоголизма, и, как результат, – замедление процесса алкоголизации населения.

Вывод. В рамках поставленной цели исследования авторами статьи предложено разработать на уровне ООН международную Конвенцию о борьбе с алкоголизацией общества, включающую международные стандарты создания соответствующих медико-социальных нормативно-правовых актов государствами-участниками предложенной Конвенции, регламентирующих меры профилактики и лечения алкоголизма на национальном уровне. Такой национальный нормативно-правовой акт должен разрабатываться органами здравоохранения будущих государств-участников предложенной Конвенции и содержать: определение понятий алкоголизации населения и алкоголизма; меры профилактики алкоголизма медико-правового характера; меры противодействия алкоголизму социально-педагогического характера со стороны образовательных, общественных и государственных организаций; меры противодействия алкоголизму запрещающего и контролирующего характер; меры противодействия алкоголизму уголовно-правового характера; нормы по условиям лечения и применения лечебных мер к лицам, больным алкоголизмом; обеспечение всеобщего доступа к информационным ресурсам данных статистического, рекомендательного, медицинского характера в сфере алкоголизации. С целью обеспечения эффективности такого нормативно-правового акта и выполнения его положений необходимо их закрепление в действующем законодательсве государств-участников предложенной Конвенции. Прежде всего, речь идет о национальном уголовном законодательстве, законодательстве об образовании, законодательстве о внутренних правоохранительных органах и законодательстве, регулируемом деятельность органов местного самоуправления.

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SUMMARY

INFLUENCE OF ALCOHOLISM AND ALCOHOLIC ADDICTION ON INCREASING THE RATE OF CRIME IN SOCIETY (MEDICAL AND LEGAL PREVENTIVE MEASURES)

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The purpose of the study is to determine universal medical and legal measures for individual and nationwide prevention of fortification of the population for practical application by developing and adopting international normative legal act – the Convention on Combating Fortification in Society. To achieve this purpose, the authors have used general scientific and special methods of cognition. Thus, the statistical method was used to analyze the data of officia statistics for 2014-2019 regarding the number of crimes committed while intoxication; the method of comparison was used in the analysis of data on studying the development of adolescents' behavior due to alcohol consumption and the effect of special programs on the prevention of alcoholism; the method of questioning was used when interviewing students of higher educational institutions regarding the prevalence of alcohol consumption among young people.

The authors of the article have offered to develop the Convention on Combating Fortification in Society, which should include binding international standards for the prevention and treatment of alcoholism in the Member States of this Convention. It has been indicated that the normative and legal acts of the future Member States of the Convention should contain: a definition of the concepts of "fortification" and "alcoholism"; medical, socio-pedagogical, criminal and other measures to counteract alcoholism; provisions for the treatment of alcohol-dependent persons; measures of universal access to information resources in the field of fortification, etc. It has been offered to amend the national regulatory acts of the Member States of the suggested Convention.

Keywords: fortification of the population, alcoholism, measures of individual prevention, measures of social prevention, medico-legal means of prevention and prophylaxes.

РЕЗЮМЕ

ВЛИЯНИЕ АЛКОГОЛИЗМА И АЛКОГОЛЬНОЙ ЗАВИСИМОСТИ НА ПОВЫШЕНИЕ УРОВНЯ ПРЕСТУПНОСТИ В ОБЩЕСТВЕ (МЕДИКО-ПРАВОВЫЕ МЕРЫ ПРОФИЛАКТИКИ)

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Цель исследования – определить для практического применения универсальные медико-правовые меры индивидуальной и общегосударственной профилактики алкоголизации населения путем разработки и принятия международного нормативно-правового акта – Конвенция о борьбе с алкоголизацией общества. Для достижения поставленной цели

использовались общенаучные и специальные методы познания: статистический метод применялся для анализа данных официальной статистики за 2014-2019 гг. относительно количества преступлений, совершенных в состоянии алкогольного опьянения; метод сопоставления применялся для анализа данных по изучению развития аддиктивного поведения у подростков вследствие потребления алкоголя и влияния специальных программ на профилактику алкоголизации; метод анкетирования применялся при опросе студентов заведений высшего образования относительно распространения употребления алкоголя среди молодежи.
Авторами статьи предложено разработать Конвенцию о борьбе с алкоголизацией общества, включающую обязательные международные стандарты профилактики и лечения алкоголизма в государствах-участниках этой Конвенции. Указано, что нормативно-правовые акты будущих государств-участников Конвенции должны содержать: определение понятий «алкоголизация» и «алкоголизм»; медицинские, социально-педагогические, уголовно-правовые и иные меры противодействия алкоголизму; положения по лечению алкогольно-зависимых лиц; меры всеобщего доступа к информационным ресурсам в сфере алкоголизации. Рекомендуется внести изменения в национальные нормативно-правовые акты государств-участников предложенной Конвенции.

რეზიუმე

ალკოჰოლიზმისა და ალკოჰოლზე დამოკიდებულების გავლენა საზოგადოებაში დანაშაულის კოეფიციენტის ზრდაზე (სამკურნალო-სამართლებრივი პრევენციული ზომები)

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კვლევის მიზანს წარმოადგენდა საყოველთაო სამედიცინო და სამართლებრივი ზომების დადგენა მოსახლეობის ალკოჰოლიზაციის ინდივიდუალური და ქვეყნის მასშტაბით პრევენციის მიზნით, საერთაშორისო ნორმატიული სამართლებრივი აქტის - საზოგადოებაში ალკოჰოლიზაციის წინააღმდეგ ბრძოლის კონვენციის შემუშავებითა და მიღებით. აღნიშნული მიზნის მისაღწევად გამოყენებულია შემეცნების ზოგადი სამეცნიერო და სპეციალური მეთოდები: სტატისტიკური მეთოდი გამოყენებული იყო 2014-2019 წწ. ნასვამ მდგომარეობაში ჩადენილი დანაშაულების სტატისტიკური მონაცემების ანალიზისთვის; შედარების მეთოდი - მოზარდებში ალკოჰოლის მოხმარების გამო ადიქციური ქცევის განვითარების შესწავლისათვის და ალკოჰოლიზმის პრევენციაზე სპეციალური პროგრამების გავლენის შესახებ მონაცემთა ანალიზისთვის; გამოკითხვის მეთოდი გამოყენებული იყო უმაღლესი საგანმანათლებლო დაწესებულებების სტუდენტების გასაუბრებისას ახალგაზრდებში ალკოჰოლის მოხმარების გავრცელების შესახებ.

სტატიის ავტორების მიერ შემოთავაზებულია საზოგადოებაში ალკოჰოლიზაციის წინააღმდეგ ბრძოლის შესახებ კონვენციის პროექტის შემუშავება, რომელიც მოიცავს სავალდებულო საერთაშორისო სტანდარტებს ამ კონვენციის წევრ სახელმწიფოებში ალკოჰოლიზმის პრევენციისა და მკურნალობის შესახებ. მითითებულია, რომ კონვენციის მომავალი მონაწილე სახელმწიფოების ნორმატიული სამართლებრივი აქტები უნდა შეიცავდეს: "ალკოჰოლიზაციის" და "ალკოჰოლიზმის" ცნების განსაზღვრას; სამედიცინო, სოციალურ-პედაგოგიური, სისხლის სამართლისა და ალკოჰოლიზმის წინააღმდეგ ბრძოლის სხვა ღონისძიებებს; დებულებებს ალკოჰოლდამოკიდებული პირების მკურნალობის შესახებ; ინფორმაციული რესურსების უნივერსალური ხელმისაწვდომობის ზომებს ალკოჰოლიზაციის სფეროში.

INFLUENCE OF SEXUAL DIMORPHISM ON THE DEVELOPMENT OF THE LOGICAL THINKING FUNCTION IN YOUNG ATHLETES AGED 13–15 YEARS WITH DIFFERENT BLOOD GROUPS

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It is known that the effectiveness of sporting activities in those athletic disciplines that require the athletes to quickly and accurately assess situations, the ability to concentrate, think correctly and make decisions in conditions of physical fatigue, mental and emotional stress (such as playing sports, tennis, sports orientation, etc.) is largely associated with the properties of basic nervous processes, which include the strength and functional mobility of nervous processes, as well as with the peculiarities of the development of basic mental functions (attention, perception, memory, thinking) [2,3,5,6,18]. For example, sports orienteering by level of aerobic energy potential of the body (maximum quantity of oxygen consumed per 1 kg of body weight) takes one of the first places among athletes, and by mental load cedes only to chess [7].

From the literature sources we find information about that the above-mentioned mental functions are an active process [15-17], and therefore they may change under the influence of training of different directions [1-14].

The results of research by L.P. Serhiynko [8] and our studies [19-21] indicate the possibility of using serological markers of blood groups in the genetic prediction of attention, perception of time, logical thinking, and visual memory of young athletes (boys). However, the identification of opportunities for the development of mental functions (in our case, logical thinking) in adolescents playing different sports, taking into account sexual dimorphism, was not carried out. The study of this problem, in our opinion, has not only theoretical but also practical interest. In particular, the knowledge about the influence of serological markers of blood groups on the development of logical thinking properties of young athletes (boys and girls) can be used in the practice of genetic psychological and pedagogical counseling of students on problems of choice of sporting and professional activities**.**

In this regard, the question of influence of serological markers of blood groups on the development of the function of logical thinking of adolescent girls-athletes specializing in athletic disciplines of various training directions remains relevant and unresolved. To the above, we can add that in one study published by us earlier an analysis of the influence of serological markers of blood groups on the development of attention [22] and of time perception [23] functions of adolescent girls-athletes has been made.

Material and methods. The study involved young girls-athletes aged 13-15 years from Brovary Higher School of Physical Culture (n=167) (experimental group), who according to classification of sports by A.G.Dembo were divided into two groups: group A (n=85) - speed and power sports (freestyle wrestling, athletics: sprinting, hurdles, jumping, shot put and discus); group B (n=82) - endurance sports (skiing, swimming: 200, 400 and 1500 m, athletics: running at 800, 1500, 3000 and 5000 m, walking). The control group of tested persons was divided into two subgroups: subgroup 1 – girls-pupils, aged 13-15 years, of Brovary Secondary School № 3 (Kyiv Region), who did not play sports (n=106); subgroup 2 – girls-first-third-year students, aged 17–20 years (n=124), of M.P.Dragomanov National Pedagogical University (n=68) and Kyiv Borys Grynchenko University (n=56), who also did not play sports.

The study of the function of logical thinking was carried out according to the method of "numerical series", which was proposed by M.V. Makarenko, V.A.Pukhov, N.V. Kolchenko and others. [4]. A tested person was given the forms with missing numbers in rows (total number of spaces - 10). He had to choose the correct numbers that should complement a row of numbers. 10 minutes were given to complete this task. In case of performance of tasks earlier than the allotted time, time of direct performance of work was registered. Quantitative indicators for assessing the function of logical thinking were as follows: 1) the number of correct answers guessed by a tested person during the work, 2) speed of thinking (in conventional units), 3) general assessment of the state of logical thinking (in points). The latter was carried out according to the scheme of the above authors [4]:

Assessment, points	6	5	4	3	2	1	0
Corrects answers, quantity	10	9	8	7	6	4–5	1–3

Speed of thinking was determined by the following formula:

$ШМ = \frac{A}{t}$, where:

Шм – speed of thinking, conventional units,

A – correct answers, number,

t – time of performance of work, minutes.

Testing was carried out in an isolated room in the first half of the day (from 9 till 12 hours, not earlier than 2 hours after a meal). One or two days before examination, the tested persons were asked to reduce the volume and intensity of their physical activity by 50%, not to take tonics and sedatives, and on the day of testing – strong tea or coffee

Data on blood groups were taken from the medical records of the persons to be tested. Individuals who did not have data on their blood group were not allowed to be tested.

In the course of the research, the significance of the difference between individuals with different blood groups of the ABO system, who represented the experimental (young athletes) and control (pupils who do not play sports) groups, was determined using the parametric Student's t-test.

The purpose of the article is to investigate the influence of serological markers of blood groups on the development of the function of logical thinking of adolescent athletes, taking into account sexual dimorphism.

Research methods: theoretical analysis and generalization of scientific and methodical literature, pedagogical monitoring, testing, methods of statistics.

Results and discussion. Materials of the comparative analysis of changes in average values of indicators of function of logical thinking of girls-athletes aged 13–15 years with different blood groups of system ABO by method "Numerical series" (without consideration of specificity of their kinds of sports) are presented in Table 1. As can be seen from the data in this table, the number of correct answers, speed of thinking and the overall assessment of this function

are significantly higher in girls with A (II) blood group compared to their age-mates with 0 (I), B (III) and AB (IV) blood group (P<0,05-0,01). No significant differences were found in the above indicators of the properties of logical thinking among people with 0 (I), B (III) and AB (IV) blood groups (P>0,05). Based on the above, we can assume that young athletes of A (II) blood group, as opposed to other age-mates, have a high associative relation with the properties of the function of logical thinking.

The following two tables (Tables 2 and 3) contain the data of a comparative analysis of changes in the average indicators of the function of logical thinking in girls who (according to the classification of sports by AG Dembo) specialize in sports with different training orientation: group A – speed and power sports, group B - endurance sports.

From the materials of the study of the function of logical thinking of girls playing speed and power sports (Table 2) no significant differences were found in the nature of changes in the above indicators (P>0,05), and therefore, in our opinion, there is no expressed associative relation with the properties of the function of logical thinking of individuals of a certain blood group.

From the analysis of the following table (Table 3) we find the data that, in our opinion, may indicate that people with A (II) blood group have the best associative relations with different properties of logical thinking. Proof of this is the significantly better average values of the three above-mentioned indicators of this function (correct answers, speed of thinking, assessment) in people with A (II) blood group compared to their sports colleagues who have 0 (I), B (III) and AB (IV) blood group (P<0,05 in all cases).

The results of the study of indicators of the function of logical thinking of pupils aged 13-15 years who do not play sports are specified in table 4. From the materials of this table we find the following: the girls with A (II) and 0 (I) blood groups have significantly better values of the mentioned function according to the registration of known indicators (correct answers, speed of thinking, assessment), and therefore by all indicators the difference between them was unreliable (P> 0,05). However, a statistically significant difference in the average values of the three mentioned indicators of logical thinking is observed, on the one hand, between individuals with A (II) and B (III) and AB (IV) blood groups (P <0,05-0,001), on the other hand - between persons with 0 (I) and B (III) and AB (IV) blood groups (P <0,05–0,001). As expected, no significant differences were found in the analysis of the average values of the thinking function between pupils with B (III) and AB (IV) blood groups (P>0,05). Thus, the above, in our opinion, may indicate that the highest indicators of development of logical thinking are specific to persons with A (II) and 0 (I) blood group, and the lowest ones - with B (III) and AB (IV) groups.

Table 1. Indicators of the function of logical thinking of girls-athletes aged 13-15 years (without taking into account the specifics of sports) with different blood groups, X±m, (n=167), conventional units

№	Blood group	n	Logic thinking		
			Correct answers, number	Speed of thinking, conventional units.	Assessment, points
1	O(I)	46	5,3±0,21	0,5±0,02	1,6±0,16
2	A(II)	48	5,9±0,22	0,6±0,03	2,1±0,17
3	B(III)	40	5,2±0,20	0,5±0,02	1,5±0,15
4	AB(IV)	33	5,1±0,24	0,5±0,02	1,5±0,16
Significance of difference		P1–P2	<0,05	<0,01	<0,05
		P1–P3	>0,05	>0,05	>0,05
		P1–P4	>0,05	>0,05	>0,05
		P2–P3	<0,05	<0,01	<0,05
		P2–P4	<0,05	<0,01	<0,05
		P3–P4	>0,05	>0,05	>0,05

Table 2. Indicators of the function of logical thinking of girls-athletes aged 13-15 years, who mainly develop the speed-power qualities (group A) with different blood groups, X±m, (n=85), conventional units

№	Blood group	n	Logical thinking		
			Correct answers, number	Speed of thinking, conventional units	Assessment, points
1	O(I)	24	5,0±0,32	0,5±0,03	1,5±0,23
2	A(II)	25	5,4±0,30	0,5±0,03	1,8±0,23
3	B(III)	20	4,8±0,30	0,5±0,03	1,3±0,20
4	AB(IV)	16	4,6±0,36	0,5±0,04	1,3±0,23
Significance of differenc		P1–P2	>0,05	>0,05	>0,05
		P1–P3	>0,05	>0,05	>0,05
		P1–P4	>0,05	>0,05	>0,05
		P2–P3	>0,05	>0,05	>0,05
		P2–P4	>0,05	>0,05	>0,05
		P3–P4	>0,05	>0,05	>0,05

Table 3. Indicators of the function of logical thinking of girls-athletes aged 13-15 years, who mainly develop the quality of endurance (group B), with different blood groups, X±m, (n=82), conventional units

№	Blood group	n	Logical thinking		
			Correct answers, number	Speed of thinking, conventional units	Assessment, points
1	O(I)	22	5,5±0,26	0,6±0,03	1,8±0,21
2	A(II)	23	6,5±0,25	0,7±0,03	2,5±0,19
3	B(III)	20	5,6±0,26	0,6±0,03	1,8±0,19
4	AB(IV)	17	5,5±0,30	0,6±0,03	1,8±0,22
Significance of difference		P1–P2	<0,05	<0,05	<0,05
		P1–P3	>0,05	>0,05	>0,05
		P1–P4	>0,05	>0,05	>0,05
		P2–P3	<0,05	<0,05	<0,05
		P2–P4	<0,05	<0,05	<0,05
		P3–P4	>0,05	>0,05	>0,05

Table 4. Indicators of the function of logical thinking of pupils aged 13-15 years, who do not play sports, with different blood groups, X±m, (n=106)

№	Blood groups	n	Logical thinking		
			Correct answers, number	Speed of thinking, conventional units	Assessment, points
1	O(I)	28	5,1±0,27	0,5±0,03	1,5±0,20
2	A(II)	30	5,3±0,26	0,5±0,03	1,7±0,21
3	B(III)	26	3,6±0,18	0,4±0,02	0,5±0,11
4	AB(IV)	22	3,5±0,18	0,4±0,02	0,5±0,11
Significance of differenc		P1–P2	>0,05	>0,05	>0,05
		P1–P3	<0,001	<0,05	<0,001
		P1–P4	<0,001	<0,05	<0,001
		P2–P3	<0,001	<0,05	<0,001
		P2–P4	<0,001	<0,05	<0,001
		P3–P4	>0,05	>0,05	>0,05

Table 5. Indicators of the function of logical thinking of 17-20-year-old female students, who do not play sports, with different blood groups, X±m, (n=124)

№	Blood group	n	Logical thinking		
			Correct answers, number	Speed of thinking, conventional units	Evaluation, points
1	O(I)	38	5,2±0,23	0,5±0,02	1,7±0,17
2	A(II)	35	5,6±0,22	0,6±0,02	1,8±0,15
3	B(III)	27	4,1±0,20	0,4±0,02	1,1±0,14
,4	AB(IV)	24	3,7±0,23	0,4±0,02	0,7±0,17
Significance of difference		P1–P2	>0,05	<0,01	>0,05
		P1–P3	<0,01	<0,01	<0,05
		P1–P4	<0,001	<0,01	<0,001
		P2–P3	<0,001	<0,001	<0,01
		P2–P4	<0,001	<0,001	<0,001
		P3–P4	>0,05	>0,05	>0,05

The indicators of mental function of logical thinking of 17-20-year-old female students having different blood groups, who do not play sports (control group, subgroup 2), are almost the same as those for the 13-15-year-old female pupils who also do not play sports (control group, subgroup 1).

As can be seen from the Table 5, significantly better average values of the mentioned mental function are registered, on the one hand, among female pupils with A (II) and B (III) and AB (IV) blood groups (P <0,01–0,001) and, on the other hand, among female students with 0 (I) and B (III) and AB (IV) blood

groups (P<0,05–0,001). Accordingly, we add that between girls with A (II) and 0 (I) blood groups, as well as between their agemates with B (III) and AB (IV) blood groups, no significant differences were found (P>0,05). Thus, we can assume that among female students who do not play sports, the best associative relation with the function of logical thinking is observed in persons with A (II) and 0 (I) blood groups, and the worst one, respectively, in persons with AB (IV) and B (III) groups.

A comparative analysis of average values of the development of logical thinking in three groups of tested persons, who had different blood groups (young athletes, pupils and students), with taking into account their sexual dimorphism is presented in Tables 6, 7 and 8.

So, it follows from the data of table 6 that by all indicators that characterize this function (correct answers, speed of thinking, evaluation) no statistically significant differences between the athletes (girls and boys) of Brovary Higher School of Physical Culture have been found (P>0,05).

Table 6. Comparative analysis of average values of the development of logical thinking in young athletes (girls and boys) of the specialized sports institutions (without taking into account the specifics of athletic disciplines) with different blood groups, X±m, (n=310)

Indicators of memory function	Statistical values	Blood groups			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Correct answers, number	X±m	n=46	n=48	n=40	n=33
		5,3±0,21	5,9±0,22	5,2±0,20	5,1±0,24
Speed of thinking, conventional units	X±m	0,5±0,02	0,6±0,03	0,5±0,02	0,5±0,02
Assessment, points	X±m	1,6±0,16	2,1±0,17	1,5±0,15	1,5±0,16
Boys (2) [9]					
Correct answers, number	X±m	n=44	n=42	n=31	n=26
		5,0±0,29	5,6±0,27	5,1±0,26	4,7±0,28
Speed of thinking, conventional units	X±m	0,5±0,02	0,6±0,03	0,5±0,02	0,5±0,02
Assessment, points	X±m	1,5±0,25	1,8±0,23	1,5±0,20	1,4±0,24
Correct answers, number	P1–P2	>0,05	>0,05	>0,05	>0,05
Speed of thinking, conventional units	P1–P2	>0,05	>0,05	>0,05	>0,05
Evaluation, points	P1–P2	>0,05	>0,05	>0,05	>0,05

Table 7. Comparative analysis of average values of development of logical thinking of pupils (girls and boys) of general educational institutions, who do not play sports, with different blood groups, X±m, (n=220)

Indicators of memory function	Statistical values	Blood groups			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Correct answers, number	X±m	n=28	n=30	n=26	n=22
		5,1±0,27	5,3±0,26	3,6±0,18	3,5±0,18
Speed of thinking, conventional unita	X±m	0,5±0,03	0,5±0,03	0,4±0,02	0,4±0,02
Evaluation, points	X±m	1,5±0,20	1,7±0,21	0,5±0,11	0,5±0,11
Boys (2) [9]					
Correct answers, number	X±m	n=32	n=34	n=25	n=23
		5,0±0,25	5,3±0,24	3,8±0,21	3,6±0,28
Speed of thinking, conventional units	X±m	0,5±0,02	0,5±0,03	0,4±0,02	0,4±0,02
Assessment, points	X±m	1,5±0,23	1,7±0,22	0,6±0,18	0,5±0,21
Correct answers, number	P1–P2	>0,05	>0,05	>0,05	>0,05
Speed of thinking, conventional units	P1–P2	>0,05	>0,05	>0,05	>0,05
Assessment, points	P1–P2	>0,05	>0,05	>0,05	>0,05

Table 8. Comparative analysis of average values of development of logical thinking in students (girls and boy) of higher educational institutions, who do not play sports, with different blood groups, X±m, (n=255)

Indicators of memory function	Statistical values	Blood groups			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Correct answers, number	X±m	n=38	n=35	n=27	n=24
		5,2±0,23	5,6±0,22	4,1±0,20	3,7±0,23
Speed of thinking, conventional units	X±m	0,5±0,02	0,6±0,02	0,4±0,02	0,4±0,02
Evaluation, points	X±m	1,7±0,17	1,8±0,15	1,1±0,14	0,7±0,17
Boys (2) [21]					
Correct answers, number	X±m	n=41	n=37	n=28	n=25
		5,3±0,22	5,5±0,23	3,6±0,17	3,5±0,16
Speed of thinking, conventional units	X±m	0,5±0,02	0,6±0,02	0,4±0,02	0,4±0,02
Assessment, points	X±m	1,7±0,17	1,8±0,19	0,6±0,11	0,4±0,10
Correct answers, number	P1–P2	>0,05	>0,05	>0,05	>0,05
Speed of thinking, conventional units	P1–P2	>0,05	>0,05	>0,05	>0,05
Assessment, points	P1–P2	>0,05	>0,05	>0,05	>0,05

As indicated by the data of a gender comparative analysis of the average values of the development of logical thinking in pupils of general educational institutions, who do not play sports (Table 7), and students of higher educational institutions, who also do not play sports (Table 8), no significant differences between boys and girls (P> 0,05) have been found. Thus, we can state that the mental features of sexual dimorphism in development of properties of logical thinking in young athletes as well as pupils and students, who do not play sports, have not been found by us.

Analyzing the nature of changes in the indicators of the function of logical thinking in young athletes, aged 13-15 years, of specialized sports institution, their age-mates – pupils of secondary schools who do not play sports, as well as older students of higher education institutions who also do not play sports, we come to the conclusion that the genetic predisposition to the development of mental traits in humans based on serological markers of blood groups of the ABO system, which was mentioned by L. P. Serhiynko [8] and evidenced by data of our previous studies involving boys-athletes [9,21], takes place.

Thus, according to the data of research of girls (without taking into account the direction of their training process) it was found that athletes with A (II) blood group have significantly better (at P <0,05-0,01) values of thinking function compared to those individuals, who have 0 (I), B (III) and AB (IV) blood groups. Almost the same nature of changes, as that in general group of female athletes (at P<0,05 in all cases), in average indicators of the mentioned function is registered in girls playing endurance sports (group B). The fact that in all respects no significant differences in values of thinking function (P>0,05) have been found in female athletes playing endurance sports (group A) is yet again an indisputable evidence of the specific impact of training loads of different orientation on the body of athletes who are different by age and sporting qualificatio [1, 10 et al.]. Based on the above, we can assume that individuals of A (II) blood group, in contrast to other individuals, have the highest associative relation with the properties of the function of logical thinking.

The results of psychophysiological studies of secondary school pupils who do not play sports indicate that individuals of not only A (II) but also 0 (I) blood groups have the best associative relation with different properties of logical thinking, and the individuals of AB (IV) and B (III) blood groups have the worst one.

Given that the genetic predisposition to the development of mental traits in humans becomes more pronounced in adulthood than in adolescence [5,10], we have conducted similar studies among students aged 17-20 (late adolescence). The latter (research), in our opinion, has become an indisputable fact that individuals with A (II) and 0 (I) blood groups have the best associative relations with different properties of logical thinking, and individuals with AB (IV) and B (III) groups, as noted earlier - the worst ones.

Theoretical and practical relevance of the work. The theoretical basis of many years research are the provisions and conclusions of a number of authors (M.N Fox, M. Khoroshukha et al., V. Lyshevska, S. Shepoval, L. Serhiynko, E. Strikalenko et al.) concerning the possibility to use serological markers of blood groups of the ABO system in genetic prediction of the development of certain somatic diseases, motor qualities and mental properties in people of different ages, genders and occupations. The practical relevance of the work consists in the possibility of psychophysiological selection of young athletes to engage in those kinds of sports for which the function of logical thinking plays an important role in the development of sportsmanship **(**for example, orienteering, tennis, playing sports, etc.) and professional selection (in particular in the choice of those professions that are based on knowledge of exact sciences).

Conclusions. The use of serological markers of blood groups according to the ABO system, in our opinion, is possible in the genetic prediction of the development of the properties of logical thinking of young people. The factor of sexual dimorphism does not make significant adjustments in the specifics of changes in the indicators of logical thinking of individuals with diffe - ent blood groups according to the ABO system. Therefore, we believe that adolescent athletes (boys, girls) and their age-mates, who do not play sports, with A (II) and 0 (I) blood groups have the best associative relations with different properties of logical thinking, and individuals with B (III) and especially with AB (IV) group – the worst ones**.**

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SUMMARY

INFLUENCE OF SEXUAL DIMORPHISM ON THE DEVELOPMENT OF THE LOGICAL THINKING FUNCTION IN YOUNG ATHLETES AGED 13–15 YEARS WITH DIFFERENT BLOOD GROUPS

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The purpose of the work is to investigate the influence of serological markers of blood groups on the development of the function of logical thinking of adolescent athletes taking into account sexual dimorphism. The study involved girls (n=167) and boys (n=143) from a specialized sports institution, who according to the classification of sports by A.G. Dembo were divided into two groups: group A - speed and power sports, group B - en-

durance sports. The control group of tested persons who did not play sports was divided into two subgroups: subgroup 1 – pupils [girls (n=106), boys (n=114)], aged 13-15 years, of secondary school; subgroup 2 – first-third year students [girls (n=124), boys (n=131)] of higher educational institutions. The study of the function of logical thinking was carried out according to the method of «numerical series» of M.V. Makarenko. Quantitative indicators for assessing the function of thinking were as follows: the number of correct answers guessed by the person during the work, the speed of thinking, the overall assessment of the state of thinking. The fact of possible use of blood groups in genetic-based prediction of development of thinking is established. It was found that girls and boys with A (II) and 0 (I) blood groups have the best associative relations with different properties of logical thinking, and individuals with AB (IV) and B (III) groups - the worst ones. It was also found that between males and females of the three groups of tested persons (young athletes, secondary school pupils, students) there are no significant differences in the average values of logical thinking, and therefore the factor of sexual dimorphism does not make significant adjustments in the specifics of changes in the above-mentioned mental function of individuals having diffe - ent blood groups.

Keywords: mental functions, logical thinking, research, sexual dimorphism, young athletes, pupils, students.

РЕЗЮМЕ

ВЛИЯНИЕ ПОЛОВОГО ДИМОРФИЗМА НА РАЗВИТИЕ ФУНКЦИИ ЛОГИЧЕСКОГО МЫШЛЕНИЯ ЮНЫХ СПОРТСМЕНОВ 13-15 ЛЕТ С РАЗНЫМИ ГРУППАМИ КРОВИ

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Цель исследования - определить влияние серологических маркеров групп крови на развитие функции логического мышления юных спортсменов подросткового возраста с учетом полового диморфизма. В исследовании приняли участие девушки (n=167) и мальчики (n=143) специализированного спортивного заведения, которые согласно классификации видов спорта А.Г. Дембо разделены на две группы: группа А – скоростно-силовые виды спорта, группа Б – виды спорта на выносливость. Контрольная группа обследованных, которые не занимались спортом, была разделена на две подгруппы: подгруппа 1 – девушки (n=106) и мальчики (n=114) в возрасте 13-15 лет, ученики общеобразовательного учебного заведения, подгруппа 2 – девушки (n=124), юноши (n=131) в возрасте 17-20 лет, студенты 1-3 курсов высших учебных заведений. Исследование функции логического мышления проводилось по методике «числовые ряды» Н.В. Макаренко. Количественными показателями оценки функции мышления являлись: количество верных ответов, угаданных лицом за время работы, скорость мышления, общая оценка состояния мышления. Установлен факт возможного использования групп крови в генетическом прогнозировании развития мышления. Выявлено, что девушки и мальчики с А(II) и 0(I) группами крови имеют наилучшие ассоциативные связи с различными свойствами логического мышления, а индивиды с АВ(IV) и В(III) группами – наихудшие. Между лицами мужского и женского пола трех групп (юные спортсмены, учащиеся общеобразовательной школы, студенты) достоверных различий в средних значениях развития логического мышления не установлено, поэтому фактор полового диморфизма не вносит существенных корректив в специфику изменений показателей данной психической функции индивидов с разными группами крови.

რეზიუმე

სქესობრივი დიმორფიზმის გავლენა ლოგიკური აზროვნების განვითარებაზე სისხლის სხვადასხვა ჯგუფის მქონე 13-15 წლის ასაკის მოზარდ სპორტსმენებში

[1]მ. ხოროშუხა, [2]ა. ბოსენკო, [3]ს. პრისიაჟნიუკი, [1]ო. ტიმჩიკი, [1]ე. ნეველომსკაია

[1]კიევის ბ.გრინჩენკოს სახელობის უნივერსიტეტი; [2]სამხრეთ უკრაინის კ.უშინსკის სახელობის ეროვნული პედაგოგიური უნივერსიტეტი; [3]ტელეკომუნიკაციების სახელმწიფო უნივერსიტეტი, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა სისხლის ჯგუფის სეროლოგიური მარკერების გავლენის განსაზღვრა ლოგიკური აზროვნების ფუნქციის განვითარებაზე მოზარდ სპორტსმენებში სქესობრივი დიმორფიზმის გათვალისწინებით. კვლევაში მონაწილეობა მიიღეს სპეციალიზებული სპორტული დაწესებულების გოგონებმა (n=167) და ვაჟებმა (n=143), რომელნიც, სპორტის სახეობათა ა.დემბოს კლასიფიკაციის მიხედვით, დაიყო ორ ჯგუფად: ჯგუფი А - სპორტის ჩქაროსნულ-ძალოვანი სახეობები, ჯგუფი В - ამტანობაზე მიმართული სპორტის სახეობები. გამოკვლეულთა საკონტროლო ჯგუფი, რომელნიც არ მისდევდნენ სპორტს, დაიყო ორ ქვეჯგუფად: ქვეჯგუფი 1 – 13 - 15 წლის გოგონები (n=106) და ვაჟები (n=114), ზოგადსაგანმანათლებლო დაწესებულებების მოსწავლეები, ქვეჯგუფი 2 – 17 – 20 წლის გოგონები (n=124) და ვაჟები (n=131), უმაღლესი საგანამანათლებლო დაწესებულებების 1-3 კურსის სტუდენტები. ლოგიკური აზროვნების ფუნქციის კვლევა ტარდებოდა ნ.მაკარენკოს “ციფრული რიგების” მეთოდიკით. ლოგიკური აზროვნების რაოდენობრივ მაჩვენებლებს წარმოადგენდა: მუშაობის დროს გამოცნობილი სწორი პასუხების რაოდენობა, აზროვნების სიჩქარე, აზროვნების მდგომარეობის ზოგადი შეფასება. დადგენილია სისხლის ჯგუფის შესაძლო გამოყენების ფაქტი აზროვნების განვითარების გენეტიკური პროგნოზირებისათვის. გამოვლენილია,რომ სისხლის А(II) და 0(I) ჯგუფების მქონე გოგონებს და ვაჟებს აქვთ ყველაზე კარგი ასოციაციური კავშირები ლოგიკური აზროვნების სხვადასხვა მახასიათებლებით, ხოლო АВ(IV) და В(III) ჯგუფების ინდივიდებს – ყველაზე ცუდი. სამი ჯგუფის (ახალგაზრდა სპორტსმენები, ზოგადსაგანამანათლებლო სკოლების მოსწავლეები, სტუდენტები) გოგონებსა და ვაჟებს შორის სარწმუნო განსხვავება ლოგიკური აზროვნების საშუალო მაჩვენებლებს შორის დადგენილი არ არის; ამიტომ სქესობრივი დიმორფიზმის ფაქტორს არ შეაქვს არსებითი კორექტივები ამ ფსიქიკური ფუნქციის მაჩვენებლების ცვლილებების სპეციფიკაში სისხლის სხვადასხვა ჯგუფის მქონე ინდივიდებში.

АНАЛИЗ РАСПРОСТРАНЕННОСТИ ХРОНИЧЕСКИХ ВИРУСНЫХ ГЕПАТИТОВ В КАЗАХСТАНЕ ЗА 2012-2016 ГГ.

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Парентеральные вирусные гепатиты В, С и Д являются одной из глобальных проблем мирового здравоохранения. Более 350 млн. единиц населения всего мира являются носителями вируса В, из них 75–160 млн. (15–40%) подвержены угрозе развития цирроза печени или гепатоцеллюлярной карциномы [1]. Ситуация с гепатитом С положительно меняется, количество инфицированных снижается, в настоящее время **страдают порядка 71 млн. лиц.** Заболеваемость инфекцией HDV снизилась в эндемичных странах в результате эффективной иммунопрофилактики против HBV и улучшения социально-экономических и гигиенических условий, однако в Азиатско-Тихоокеанском регионе по сей день остается актуальной причиной заболеваемости [2,3]. Гепатит В с дельта-агентом является серьёзной проблемой и в Республике Казахстан. Статистика распространённости HDV по сей день уточняется. HDV-инфекция повышает риск развития гепатоцеллюлярной карциномы (ГЦК) в три раза и смертности в два раза у пациентов с HBsAg-позитивным циррозом печени. Согласно исследованиям [4,5], постоянная репликация HDV приводит к циррозу и ГЦК в годовом исчислении 4% и 2,8%, соответственно, и является предиктором печёночной смерти.

Цель исследования – анализ распространенности вирусных гепатитов в Республике Казахстан за 2012-2016 гг.

Материал и методы. В исследовании применены показатели описательной статистики Научно-практического центра «Санитарно-эпидемиологической экспертизы и мониторинга» Комитета по защите прав потребителей Министерства Национальной экономики Республики Казахстан и Комитета статистики Министерства Национальной экономики РК.

Республика Казахстан относится к странам с высокой эндемичностью по вирусному гепатиту В (более 8%) [5]. Согласно экспертным оценкам, в Республике Казахстан скрининговые исследования в группах риска в 2014 г. выявили наличие HBsAg у 2,3% населения. Среди беременных и доноров крови распространенность вирусного гепатита В (ВГВ) составила 1,3% в 2013 г. и 1,2% - в 2014 г. К значительным успехам в борьбе с ВГВ в Республике Казахстан привело введение в календарь профилактических прививок вакцинации против гепатита В. В результате заболеваемость снизилась почти в 40 раз: с 29,3 в 1997 г. до 0,8 на 100 000 населения в 2014 г. За последние 20 лет уровень заболеваемости снижен в 23,7 раз, а среди детей - в 52 раза [6].

Несмотря на проводимые эффективные меры, количество выявляемых микст вирусов возрастает, в число которых входит и гепатит В с дельта агентом [7]. Исследования 5-летнего среза показали, что заболеваемость хроническим вирусным гепатитом В (ХГВ) в Казахстане в целом имеет тенденцию к спаду [7]. Количество заболеваний ХГВ в 2012 году составило 35,4 случаев на 100 тыс. населения, в 2016 г. данная цифра уменьшилась на 5,8 случаев (↓16,4%) и составила 29,6 заболеваний на 100 тыс. населения. В течение рассматриваемого периода существенное снижение случаев ХГВ зарегистрировано в 2015 г. - 27,9 на 100 тыс., которое далее сопровождалось незначительным ростом заболеваемости в 2016 году на 6% или 1,7 случаев на 100 тыс. населения (рис 1).

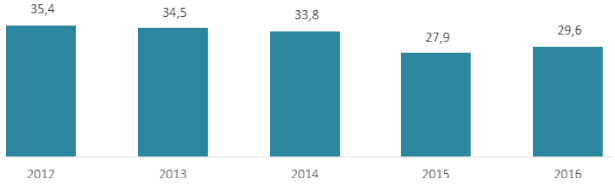

Рис. 1. Заболеваемость ХГВ, на 100 тыс. населения в период с 2012 по 2016 гг.

Примечательно, что заболеваемость ХГВ среди детей и подростков существенно сократилась. Так, в 2012-2016 гг. дети до 14 лет болеют ХГВ 3,7 раза меньше (с 6,3 до 1,7 случаев на 100 тыс.), а подростки 15-17 лет - в 4,8 раза (с 22,4 до 4,7 случаев на 100 тыс.).

По итогам 2016 г. заболеваемость ХГВ с дельта агентом составила 0,39 случаев на 100 тыс. населения (рис. 2).

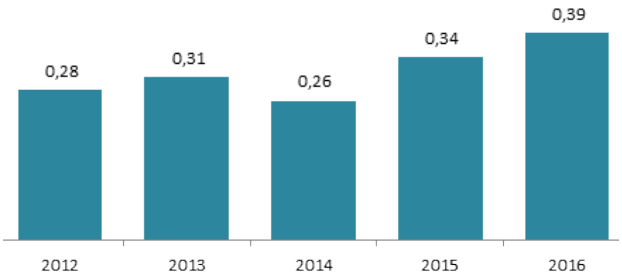

Рис. 2. Заболеваемость ХГВ с дельта агентом, на 100 тыс. населения в период с 2012 по 2016 гг.

Сравнительно с общим показателем заболеваемости гепатитом В, рост заболеваемости ХГВ с дельта агентом небольшой, однако статистика проявляет увеличение случаев заболеваемости. Так, за последние 5 лет заболеваемость ХГВ с дельта агентом увеличилась на 40% с 0,28 до 0,39 случаев на 100 тыс. н. Причем в 2015 и 2016 годах темп роста высок 31% и 13%, соответственно.

Следует отметить, что случаи заболеваемости ХГВ с дельта агентом чаще встречаются среди населения старше 18 лет. Заслуживает внимания, что ХГВ с дельта агентом практически не встречается среди детей, а заболеваемость среди подростков 15-17 лет стремительно падает с 0,38 случаев, впервые выявленных на 100 тыс. населения в 2012 году до нуля в 2016 г. (рис. 3).

Согласно данным последних эпидемиологических исследований, распространенность инфекции вируса гепатита С, оцененная на основании выявления anti-HCV, варьировать в зависимости от региона, однако по стране в целом распространенность составляет 3,1%. [8]. В пересчете на население страны в 2013 г. количество пациентов с положительным тестом на anti-HCV составило 483 тыс. человек.

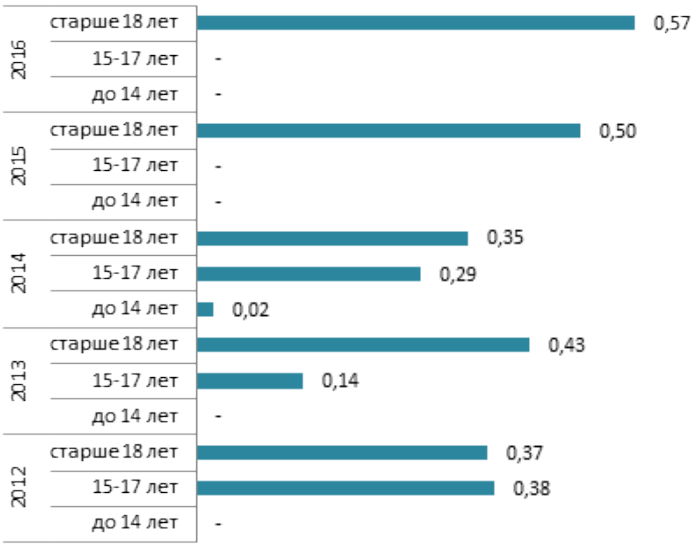

Рис. 3. Случаи заболеваемости ХГВ с дельта агентом с учетом основных возрастных групп на 100 тыс. населения

Таблица 1. Распространённость antiHCV в Республике Казахстан в 2013 г.

Год	Распространенность antiHCV	Всего случаев
2013 – среди всех возрастов	3.1%	483,280

Рис. 4. Распространенность ВГС в Казахстане: распределение по полу и возрасту. Статистические данные представлены по материалам Нерсесова А.В. [6]

Рис. 5. Показатели заболеваемости ВГС в Казахстане с учетом возраста. Статистические данные представлены по материалам Нерсесова А.В. [6]

Среди них виремия встречалась почти у 75%. При пересчете количества пациентов на население страны обнаруживается, что распространённость виремии, т.е. хронической инфекции гепатита С в Казахстане составляет 2,4%, что соответствует 362 тыс. пациентов в 2013 г. Распространенность вирусного гепатита С оценивалась на основании применения к общей популяции данных о распространенности в Алматы 3.0% и в Южно-Казахстанской области 4.6%. Распространенность, в среднем, составила 3.9% среди населения в возрасте 18–69 лет [6], таблица 1, рис 4 и 5.

Изучение факторов, способствующих усилению трансформации вирусных гепатитов в цирроз и гепатоцеллюлярную карциному, является значимым направлением в гепатологии. Так, известно влияние на прогрессирование фиброза употребления алкоголя, высокой вирусной нагрузки, возраст, мужской пол, позитивный HbeAg, коинфекция с вирусами гепатита D и C , вирусом иммунодефицита человека (ВИЧ) [11].

Среди изучаемых факторов развития цирроза и гепатоцеллюлярной карциномы на сегодняшний день актуальными являются следующие метаболический синдром, нарушение толерантности к глюкозе и дефицит витамина Д. Инсулинорезистентность ассоциируется с усилением воспалительно-некротических изменений печени и формированием стеатоза [12]. Влияние стеатоза на течение хронического вирусного гепатита В недостаточно изучено. По данным различных авторов [20], распространённость случаев стеатоза печени при ХГВ составляет от 27 до 51%, до конца не определена его роль в прогрессировании фиброза и цирроза печени. Ассоциация дельта гепатита со стеатозом практически не изучена.

Неалкогольную жировую болезнь печени (стеатоз/стеатогепатит) расценивают как печеночную манифестацию метаболического синдрома. В исследованиях по изучению роли витамина D у больных ожирением установлено, что с дефицитом витамина D (<10 ng/mL) ассоциирован более высокий риск развития инсулинорезистентности, метаболического синдрома, артериальной гипертензии и сахарного диабета [13]. К биологическим функциям витамина D относят торможение клеточной пролиферации и ангиогенеза, ингибирование продукции ренина, стимуляцию продукции инсулина и кателицидинов. Получены доказательства того, что низкий уровень витамина D может рассматриваться как независимый предиктор ожирения. В свою очередь ожирение может способствовать снижению уровня циркулирующего в крови витамина D за счет повышенного его захвата жировой тканью. Сообщается, что витамин D является значимым компонентом иммунного модулятора инфекции вируса гепатита С и метаболического заболевания печени. У больных ХГС выявлена тенденция более быстрого прогрессирования фиброза на фоне дефицита витамина D [14].

В Республике Казахстан около 90% населения имеют дефицит витамина D, однако проблема по сей день остаётся малоизученной. Имеются единичные исследования по распространённости - исследование Пушкарёва В.К. и соавт., проведенное в г. Алматы показало, что среди 1387 подростков в возрасте от 10 до 15 лет дефицит витамина D выявлен у более 70% детей, из которых выраженный дефицит диагностирован у 31,5% обследуемых [15]. Что касается HBV-инфицированных пациентов, связь между уровнем витамина D, вирусной нагрузкой HBV и дисфункцией печени остается в значительной степени неясной, что диктует необходимость исследования роли витамина D в формировании инсулинорезистентности, исходах противовирусной терапии и прогрессировании фиброза у больных вирусными гепатитами. В Республике Казахстан диагностические возможности для пациентов с заболеваниями печени улучшаются. Внедрены методы определения количественной вирусной нагрузки HDV, измерения уровня витамина D, во всех регионах имеется доступ к неинвазивной оценке степени фиброза. Среди визуализационных методов исследования используются компьютерная и магнитно-резонансная томографии, протонная МР-спектроскопия, являющаяся единственным методом, позволяющим неинвазивно оценить количественное содержание триглицеридов в печени [18].

Согласно последним практическим рекомендациям Европейской ассоциации по изучению заболеваний печени, транзиентная эластометрия может считаться стандартом неинвазивного теста для измерения эластичности печени (уровень доказательности – А1), имеет высокую достоверность при вирусных гепатитах (А1), менее достоверна при неалкогольной жировой болезни печени и других хронических заболеваниях печени (А1), обладает более высокой чувствительностью при обнаружении цирроза, чем при выявлении «продвинутых» стадий фиброза (А1). Внедрение датчика XL+Probe позволило исследовать жесткость печени у пациентов с ожирением и толщиной подкожной клетчатки до 3,5 см и снизить частоту неудач у больных с ИМТ > 30 кг/м^2, ранее варьирующую от 3 до 16% [19]. Однако, диагностическая точность и значимость датчика при комбинированном поражении печени (вирусный гепатит на фоне жирового гепатоза) недостаточна ясна и требует дальнейших исследований.

При исследовании данных региональных Гепатологических центров в 2016 г. скрининговое фибросканирование фиброз на поздних стадиях выявляется в группе пациентов с хроническим вирусным гепатитом В с дельта агентом. Распределение пациентов с ХВГ с дельта агентом по степени фиброза печени показало, что в основном пациенты диагностируются при стадии фиброза F3-F4. Практически во всех макрорегионах доля пациентов в стадии F3-F4 фиброза печени составляет больше половины всех наблюдаемых (рис. 6).

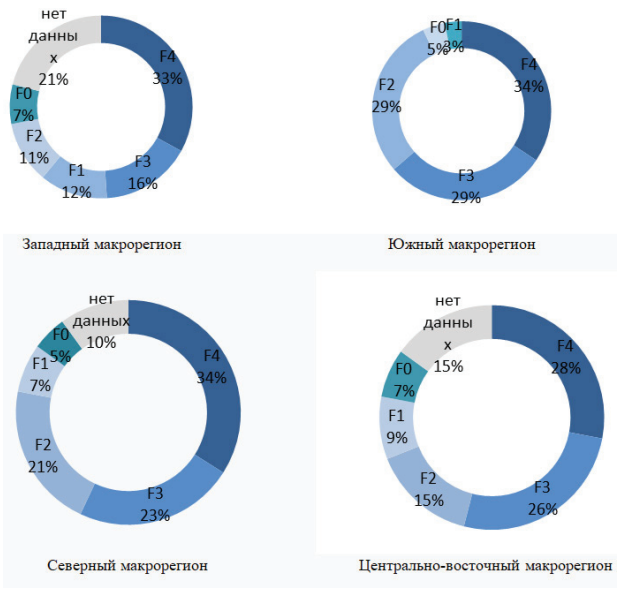

Рис. 6. Распределение по макрорегионам

Целью терапии хронического гепатита В является улучшение прогноза пациента через устойчивое ингибирование вирусной репликации. Однако имеет место неопределенность и потенциально неограниченная продолжительность курса лечения аналогами нуклеозидов. Во время лечения также возникают вопросы об устойчивости и безопасности, финансовых затратах и приверженности пациента. Ингибирование ДНК считается «удовлетворительной конечной точкой», а отмена препарата все еще приводит к высоким показателям рецидивов. Клиренс поверхностного антигена гепатита В (HBsAg) является «идеальной конечной точкой» для решения вопроса о прекращении лечения и влияния на прогноз. В последнее время применение «Оптимизированной стратегии противовирусного лечения» позволило повысить уровень клиренса HBsAg и сделать возможной «идеальную конечную точку».

ВОЗ полагает, что элиминация гепатита С возможна и реально достижима, однако доступ к лечению HBV и HCV все еще недостаточный. Вакцины против HCV по сей день не существует, однако гепатит С можно излечить относительно быстро с использованием высокоэффективных противовирусных препаратов прямого действия. В “Глобальном докладе ВОЗ о гепатите в 2017 г.” продемонстрировано, что ряд стран предпринимают успешные шаги в борьбе с гепатитами. В Египте увеличение продукции генерических противовирусных препаратов привело к снижению цены на трехмесячный курс лечения гепатита С с 900 долларов США в 2015 г. до менее 200 долларов США в 2016 году. В Пакистане курс лечения стоит в настоящее время около 100 долларов США. В Монголии средства для лечения HBV и HCV включены в Национальную систему медицинского страхования.

В Казахстане с 2018 года основой лечения хронического вирусного гепатита С является комбинированная противовирусная терапия препаратами софосбувир/даклатасвир. С 2018 г. через международную организацию ЮНИСЕФ закуплен ***препарат тенофовир для обеспечения в рамках гарантированного объёма бесплатной медицинской помощи.*** С 2019 г. Казахстан включен в добровольную лицензию на инновационные препараты от гепатита С, подписание меморандума позволяет казахстанским пациентам получить более широкий доступ к лечению. Планируемый объем закупок препаратов позволит приблизить Казахстан к цели стать страной, где гепатит С элиминирован.

В Республике Казахстан предпринимаются достаточно эффективные меры по борьбе с вирусными гепатитами. Введение в календарь профилактических прививок вакцинации против гепатита В привело к значительному снижению заболеваемости среди населения младше 18 лет. Однако наблюдается рост заболеваемости дельта гепатитом, к примеру за период с 2012 по 2016 гг. заболеваемость ХВГ с дельта лиц старше 18 лет выросла на 50% и составила 0,57 случаев на 100 тыс. С учётом поздней выявляемости HDV, высокого риска канцерогенеза, отсутствия эффективного лечения дельта-гепатит становится наиболее опасным вирусным поражением печени и требует активации профилактических мер путём внедрения экспресс-тестов и усиления эпидемиологического контроля. С увеличением доступа к высокоактивным противовирусным агентам и прогнозируемой элиминации гепатита С, актуальным становится вопрос изучения стеатоза печени, в связи с возрастающим глобальным ростом метаболических нарушений.

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SUMMARY

ANALYSIS OF PREVALENCE OF CHRONIC VIRAL HEPATITIS IN KAZAKHSTAN IN 2012-2016

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The introduction of vaccinations against hepatitis B into the preventive vaccination calendar has led to a significan decrease in the incidence of viral hepatitis B among the population under 18 years of age. The goal is to analyze the effec of viral hepatitis in the Republic of Kazakhstan.

Our studies of a 5-year cross-section showed that the incidence of chronic viral hepatitis B tends to decline. So, if the number of CHB diseases in 2012 was at the level of 35.4 cases per 100 thousand population, then in 2016 this figur decreased by 5.8 cases (↓ 16.4%) and amounted to 29.6 diseases per 100 thousand. During the period under review, a significant decrease in CHB cases was recorded in 2015 (27.9 per 100 thousand people), which was further accompanied by a slight increase in the incidence in 2016 by 6% or 1.7 cases per 100 thousand people.

However, there is an increase in the incidence of delta hepatitis, for example, for the period from 2012 to 2016, the incidence of CVH from delta of citizens over 18 years old increased by 50% and amounted to 0.57 cases per 100 thousand people. According to recent epidemiological studies, the prevalence of hepatitis C virus infection (estimated from anti-HCV detection) may vary by region, but the prevalence is 3.1% nationwide. In terms of the population of the country in 2013, the number of patients with a positive test for anti-HCV was 483 thousand people. Among them, viremia occurs in almost 75% of people. If we recalculate this number of patients per population of the country, we will see that the prevalence of viremia, i.e. the prevalence of chronic hepatitis C infection in Kazakhstan is 2.4%, which corresponds to 362 thousand patients in 2013.

Taking into account the increase in access to highly active antiviral agents in the Republic of Kazakhstan, the paradigm of predicted elimination of hepatitis C is presented. The issue of studying liver steatosis becomes relevant, in connection with the increasing global growth of metabolic disorders, including in the Republic of Kazakhstan.

Keywords: chronic hepatitis B, hepatitis D, chronic hepatitis C, Republic of Kazakhstan, liver fibrosis, steatosis

РЕЗЮМЕ

АНАЛИЗ РАСПРОСТРАНЕННОСТИ ХРОНИЧЕСКИХ ВИРУСНЫХ ГЕПАТИТОВ В КАЗАХСТАНЕ ЗА 2012-2016 ГГ.

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Цель исследования – анализ распространенности вирусных гепатитов в Республике Казахстан за 2012-2016 гг.

В исследовании применены показатели описательной статистики НПЦ «Санитарно-эпидемиологической экспертизы и мониторинга» Комитета по защите прав потребителей Министерства Национальной экономики Республики Казахстан и Комитета статистики Министерства Национальной экономики РК.

Введение в календарь профилактических прививок вакцинации против гепатита В в Республике Казахстан привело к значительному снижению заболеваемости среди населения младше 18 лет. Результаты исследования за 2012-2016 гг. период показали, что заболеваемость хроническим вирусным гепатитом В имеет тенденцию к спаду. Количество заболеваний хроническим гепатитом В (ХГВ) в 2012 году насчитывало 35,4 случаев на 100 тыс. населения, а в 2016 г. показатель уменьшился на 5,8 (16,4%) и составил 29,6 случаев на 100 тыс. населения. В течение рассматриваемого периода самый существенный спад случаев ХГВ зарегистрирован в 2015 г. (27,9 на 100 тыс. населения), затем в 2016 г. происходит незначительный рост случаев заболеваемости на 1,7 (6%) случаев на 100 тыс. С 2012 по 2016 гг. наблюдается рост случаев заболеваемости дельта гепатитом лиц старше 18 лет на 50%, что составило 0,57 случаев на 100 тыс. населения. Согласно данным последних эпидемиологических исследований, распространенность инфекции гепатита С, на основании обнаружения anti-HCV, варьировала в зависимости от региона, однако по стране в целом распространенность составила 483 (3,1%) тыс. больных.

Авторами представлена парадигма прогнозируемой элиминации гепатита С. На сегодняшний день весьма актуальным является изучение стеатоза печени в связи с возрастающим глобальным ростом метаболических нарушений в Казахстане.

რეზიუმე

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კვლევაში გამოყენებულია "სანიტარულ-ეპიდემიოლოგიური ექსპერტიზის და მონიტორინგის ცენტრის" აღწერილობითი სტატისტიკის მაჩვენებლები.

ყაზახეთის რესპუბლიკაში B ჰეპატიტის საწინააღმდეგო ვაქცინაციის შეტანამ პროფილაქტიკური აცრების კალენდარში განსაზღვრა ავადობის მნიშვნელოვანი შემცირება 18 წლამდე ასაკის მოსახლეობაში. 5-წლიანი პერიოდის კვლევის შედეგებმა ცხადყო, რომ ქრონიკული ვირუსული B ჰეპატიტით ავადობას აქვს შემცირების ტენდენცია. ქრონიკული B ჰეპატიტით დაავადების რაოდენობა 2012 წელს იყო 35,4 შემთხვევა 100 000 მოსახლეზე, ხოლო 2016 წელს ეს მაჩვენებელი შემცირდა 5,8-ით (16,4%) და შეადგინა 29,6 შემთხვევა 100 000 მოსახლეზე.

განხილულ პერიოდში ქრონიკული B ჰეპატიტის შემთხვევების ყველაზე მნიშვნელოვანი შემცირება აღინიშნა 2015 წელს (27,9 შემთხვევა 100 000 მოსახლეზე); შემდეგ, 2016 წელს ავადობამ უმნიშვნელოდ იმატა – 1,7-ით (6%) 100 000 მოსახლეზე. 2012-2016 წწ. აღინიშნა დელტა ჰეპატიტით ავადობის შემთხვევების ზრდა 50%-ით 18 წელზე მეტი ასაკის პირებში, რამაც შეადგინა 0,57 შემთხვევა 100 000 მოსახლეზე. ბოლო ეპიდემიოლოგიური კვლევების მონაცემების მიხედვით, C ჰეპატიტის ინფექციის გავრცელება (ანტი-HCV-ს აღმოჩენის საფუძველზე) ვარირებს რეგიონებს შორის, თუმცა, მთლიანობაში ქვეყანაში გავრცელებამ შეადგინა 483 000 (3,1%) პაციენტი.

ავტორების მიერ მოცემულია C ჰეპატიტის პროგნოზირებადი ელიმინაციის პარადიგმა. დღევანდელ დღეს აქტუალურია ღვიძლის სტეატოზის შესწავლა მეტაბოლური დარღვევების ზრდის გლობალურ ზრდასთან დაკავშირებით ყაზახეთში.

EPIGENETIC MODIFICATION UNDER THE INFLUENCE OF PEPTIDE BIOREGULATORS ON “AGED” HETEROCHROMATIN

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Following the completion of the Human Genome Project, the strategic direction of modern genetics moved toward functional genomics. This field is concerned with the functions of mapped genes, determining the functions of DNA located in non-coding areas, and developing new technologies for the comparative analysis of gene expression. Non-coding DNA, often comprising repetitive sequences of nucleotides, is localized in heterochromatin. There are various types of heterochromatin, including structural and facultative heterochromatin, nucleolar organizer region (NORs) heterochromatin, and telomeric heterochromatin. However, the functions of heterochromatin remain largely unclear.

Facultative heterochromatin - heterochromatinization chromatin (condensed euchromatin or heterochromatin regions, which mainly consist of “closed” - transcribable genes) occur in aging [4,5] and are generally hypoacetlated and methylated indicating of an epigenetic change [1,11,14]. Hypermethylation causes heterochromatinization and thus results in gene silencing [12]. The fact that such histone modifications are reversible – offers potential usage in therapy [15].

In the present investigation are considered eligible the modification of heterochromatin (total heterochromatin, constitutive – pericentromeric and telomeric heterochromatin, nucleolus organizer regions (NORs) heterochromatin and facultative heterochromatin) under the influence of peptide bioregulators (tetrapeptides: Ala-Glu-Asp-Gly -Epitalon; Lys-Glu-Asp-Ala – Livagen; Ala-Glu-Asp-Pro - Cortagen and dipeptide Lys-Glu - Vilon) in lymphocyte cultures of healthy individuals, aged 20-88 years.

Material and methods. We used molecular-cytogenetic methods. We studied chromosomes in 40 lymphocyte cultures obtained from 20 healthy individuals of 75-88 years and 10 cultures from young 10 individuals - 20 to 40 years. In lymphocyte cultures were studied: total heterochromatin (differential scanning calorimeter); constitutive heterochromatin (activity of ribosomal genes of acrocentric chromosome – NORs, pericentromeric C-heterochromatin (C-band) and telomeric heterochromatin) and facultative heterochromatin (sister chromatid exscanges – (SCE) with 5-bromdeoxyuridin (BrdU) [8].

Description of the preparations

Epithalon (Ala-Glu-Asp-Gly) reinforces the organism’s resistance to stresses, regulating neuro-endocrine system and prolongs the average life expectancy;

Livagen (Lys-Glu-Asp-Ala) increases the average level of protein synthesis in aging, renovates liver proteins and induces the activation of protein synthesis in hepatocytes;

Cortagen (Ala-Glu-Asp-Pro) in humans demonstrated a pronounced therapeutic effect on the structural and functional recovery of the damaged peripheral nerve tissue;

Vilon (Lys-Glu) stimulates lowering for the risk of premature aging, has an antitumor activity and stimulates functioning of the immune system and reparative processes, strengthens the resistance of organisms to stress activities, favors prolongation of the average life span [3].

The bioregulators kindly was provided by professor Vladimir Khavinson (Institute Bioregulation and Gerontology, St. Petersburg, Russia).

Results and discussion. *Differential Scanning calorimeter*

The heat absorption curves corresponding to denaturation processes in intact lymphocytes and in lymphocyte cultures treated by peptides (Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala, Ala-Glu-Asp-Pro, and Lys-Glu) indicate that the treatment of cells with peptides induced heat redistribution and should be attributed to the local decondensation (deheterochromatinization) of loops of up to the 30 nm fibers and partial decondensation of

transcribed chromatin transformation of 10 nm filaments into 5 nm filaments in old individuals (75-88 years) in comparison with young - 20-40 years individuals. Thus, we can conclude that the peptide bioregulators (Ala-Glu-Asp-Gly; Ala-Glu-Asp-Pro, Lys-Glu-Asp-Ala and Lys-Glu) unfolds the highest levels of chromatin organization, that induces deheterochronatinization of total (structural and facultative) chromatin in intact cells of old individuals (Table).

Variability of facultative heterochromatin based on the SCE test. The results of studies on the induction of SCEs by peptide bioregulators (tetrapeptides: Ala-Glu-Asp-Gly, Lys-Glu-Asp-Ala, Ala-Glu-Asp-Pro and dipeptide Lys-Glu) in lymphocyte cultures of aged individuals are shown in Table. The analysis showed that Epitalon induced a significant increase in SCE counts in A, C, D and G group chromosomes. Epitalon-treated cells from old individuals corresponding to an average of 8.4±0.5 SCE/per cell (for intact cultures of the same individuals, this value was 5.9±0.2 SCE/cell); Livagen (Lys-Glu-Asp-Ala) induced a significant increase in SCE counts in A, B, C, D, E and G group chromosomes with statistic relevance (an average of 9.2±0.4 SCE/cell); Cortagen (Ala-Glu-Asp-Pro) significantly increased SCE counts in A, C and D group chromosomes (an average of 10.1±0.3 SCE/cell) in comparison with intact cells and the bioregulator Vilon (Lys-Glu) significantly increased SCE counts in A, C, D, E and G group chromosomes (an average of 9.9±0.6 SCE/per cell).

This data indicates that each of the studied peptide bioregulators has a selective effect on definite chromosomes. Higher level of SCEs (deheterochromatinization) were registered in telomeric heterochromatin and dicreased (heterochromatinization) in the medial regions of chromosome arms; The SCE processes do not occur or are less in heterochromatin or heterochromatinized chromosome regions. Therefore, the increased frequency of SCEs under the influence of bioregulators demonstrates the decondensation (deheterochromatinization) of the condensed during the aging chromosome regions, followed by the release of the repressed genes located there [10,13].

Transcriptional activity of ribosomal genes.

The associative activity of the strands of acrocentric chromosomes positively correlates with the intensity of Ag-staining that depends on the activity of the ribosomal genes located in NORs. The absence of silver staining (caused by condensation of the stalks) also testifies to the inactivation of ribosomal genes.

The data obtained from the analysis of Ag-positive NORs in cultured lymphocytes, intact and treated with bioregulators, obtained in the case of old donors, are shown in the Table. It was shown that peptide bioregulators (Ala-Glu-Asp-Gly, Lys-Glu-Asp-Ala, Ala-Glu-Asp-Pro, and Lys-Glu) strongly increased the amount of Ag-positive NORs in all acrocentric chromosomes involved or not involved in associations, in comparison with intact cells ($p<0.001$). In particular, the number of Ag-positive NORs of acrocentric chromosomes involved in association corresponded to 2.32±0.12 for Epitalon; to 2.49±0.14 for Livagen; to 2.20±0.11 for Cortagen and 2.39±0.11 for Vilon; for per bioregulator - treated cells, this data is significantly higher than the corresponding index for intact culture cells (Table). Our results are in accordance with the previous data [8]. In particular, hormones, various growth factors and chemicals induced chromosome decondensation (in old age as well) resulting in increased transcriptional activity of nucleolar organizer regions [7,8]. An increase in the amount and size of Ag-positive NORs, and an increase in the number of acrocentric chromosomes involved in associations in the cultures obtained from old individuals and treated with peptide bioregulators, indicated deheterochromatinization of satellite stalks, when compared with control values. This can lead to the intensification of protein synthesis because of the activation of ribosomal genes in aged individuals [2,6].

Heteromorphism of structural pericentromeric C-heterochromatin. The data on heteromorphism of structural pericentromeric heterochromatin (C-segments) in intact lymphpcytes and in lymphpcytes treated by peptide bioregulators (Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala, Ala-Glu-Asp-Pro, and Lys-Glu) of old individuals for chromosomes 1, 9 and 16 are presented in the Table.

The data reflectin variability of large (d and e) and small (a and b) C-segment variant frequencies in separate chromosomes appeared to be equal in the case of the tested bioregulators. It should be noted that in the cells, treated with Cortagen (Ala-Glu-Asp-Pro) and Vilon (Lys-Glu), the distribution of C-segment variants for chromosomes 1, 9 and 16 remained stable and did not differ in old people ($p>0.05$).

Table. Influence of peptide bioregulators (Epitalon, Livagen, Cortagen and Vilon) on reactivation of chromatin from old individuals

Experimental conditions	Association of acrocentric chromosomes per cell	Facultative heterochromatin (SCE per cell)	Total heterochromatin	Structural heterochromatin(C- bends) Chromosomes		
				1	9	16
Control (20-40yr.)	1.33±0.06	7.7±0.4	Stable condition	Stable condition	Stable condition	Stable condition
Control (75-88yr.)	1.17±0.05	5.9±0.2	Heterochromatinized	Heterochromatinized	Stable condition	Stable condition
Epitalon	2.32±0.12	8.4±0.5	Deheterochromatinized	Deheterochromatinized	Deheterochromatinized	Stable condition
Livagen	2.49±0.14	9.2±0.4	Deheterochromatinized	Deheterochromatinized	Deheterochromatinized	Stable condition
Cortagen	2.20±0.11	10.1±0.3	Deheterochromatinized	Heterochromatinized	Stable condition	Stable condition
Vilon	2.39±0.11	9.9±0.6	Deheterochromatinized	Heterochromatinized	Stable condition	Stable condition

Chromosome 1 and 9 appeared to be deheterochromatinized (the decrease of large bands in size) in Epitalon and Livagen- treated cells. The rate of heteromorphism for appointed chromosomes was significant ($p<0.001$). A differenc from the control indices was not noticed for chromosome 16. It should be noted that in the cells, treated with Cortagen (Ala-Glu-Asp-Pro) and Vilon (Lys-Glu) (Table), large and small C-segment variants in chromosomes were registered with approximately the same <frequency in intact cells, and differences between the indices compared were not significant (Table). The results indicated that each peptide bioregulator selectively deheterochromatinizes 1, 9 and 16 chromosome C-segment variants.

Conclusion. Epigenetic process – heterochromatinization progress with aging and can deactivate many previously functioning active genes. It blocks certain stages of normal metabolic processes in the cell, which inhibits many specifi enzymes and leads to aging pathologies. The action of genetic systems reveals general rules in the behavior of such systems, such as the connection between the structural and functional interrelationships between the "directing" and "directed" structures. In this respect, it should be noted that heterochromatinised regions in chromosomes can reversed by many physical and chemical agents, hormones and peptide bioregulators [5,7,9]. Peptide bioregulators (tetrapeptides: Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala, Ala-Glu-Asp-Pro, and dipeptide Lys-Glu) generally affects the remodeling of facultative heterochromatin (deheterochromatinization). Peptide bioregulators induce: 1. Unrolling -deheterochromatinization of total heterochromatin, constitutive (pericentromeric, telomeric, and nucleolar organizer regions (NOR)) and facultative heterochromatin; 2. Higher level of SCEs (deheterochromatinization) were registered in telomeric heterochromatin and decreased (heterochromatinization) in the medial regions of chromosome arms; 3. Each peptide bioregulator selectively deheterochromatinizes a specific region of chromosomes releasing inactive (once active) genes, which, apparently, can contributes to the targeted treatment of aging diseases.

The proposed genetic mechanism responsible for constitutive and facultative heterochromatin remodeling (deheterochromatinization) of old age may lead for the prolongation of the life span and to the development strategy of therapeutic treat of the aging pathologies.

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SUMMARY

EPIGENETIC MODIFICATION UNDER THE INFLUENCE OF PEPTIDE BIOREGULATORS ON "AGED" HETEROCHROMATIN

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Following the completion of the Human Genome Project, the strategic direction of modern genetics has moved toward functional genomics, to explore the functions of non-coding regions of DNA. These non-coding regions are localized in heterochromatin. The functions of heterochromatin largely remain unclear. Facultative heterochromatin occurs in aging.

The effe t of synthetic peptide bioregulators (tetrapeptides: Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala; Ala-Glu-Asp-Pro and dipeptide - Lys-Glu) on total heterochromatin, constitutive (structural) and facultative heterochromatin in cultured lymphocytes of individuals aged 75-88 and 20 - 40 years have been studied.

We used a molecular-cytogenetic methods: differential scanning calorimetry; activity of ribosomal genes of acrocentric chromosome satellite stalks – NORs; C-heterochromatin; sister chromatid exchanges (SCE).

The results showed that peptide bioregulators: 1. induce unrolling - deheterochromatinization of total heterochromatin, constitutive (pericentromeric, telomeric, and nucleolar organizer

regions (NOR)) and facultative heterochromatin; 2. induce higher level of SCEs (deheterochromatinization), were registered in telomeric heterochromatin and decreased (heterochromatinization) SCEs level in the medial regions of chromosome arms; 3. each peptide bioregulator selectively deheterochromatinizes a specific region of chromosomes releasing inactive (once active) genes, which, apparently, can contribute to the targeted treatment of aging diseases.

The proposed genetic mechanism responsible for the remodeling of constitutive and facultative heterochromatin emphasizes the importance of external and internal factors in the development of diseases and may lead to the development of a strategy for the therapeutic treatment of senile pathology.

Keywords: association, acrocentric chromosomes, bioregulators, heterochromatin, NOR, SCE.

РЕЗЮМЕ

ЭПИГЕНЕТИЧЕСКАЯ МОДИФИКАЦИЯ ГЕТЕРОХРОМАТИНА ПРИ СТАРЕНИИ ПОД ДЕЙСТВИЕМ ПЕПТИДНЫХ БИОРЕГУЛЯТОРОВ

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После завершения проекта «Геном человека» стратегическое направление современной генетики переместилось в сторону функциональной геномики. Эта область связана с изучением функций картированных генов, определением функций ДНК, расположенных в некодирующих областях. Некодирующая ДНК, часто содержащая повторяющиеся последовательности нуклеотидов, локализована в гетерохроматине. Функции гетерохроматина в значительной степени остаются неясными.

Изучено влияние синтетических пептидных биорегуляторов (тетрапептиды: Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala; Ala-Glu-Asp-Pro и дипептид Lys-Glu) на общий гетерохроматин, конститутивный (структурный) и факультативный гетерохроматин в культивируемых лимфоцитах лиц в возрасте 75-88 и 20-40 лет.

Использованы молекулярно-цитогенетические методы - дифференциальная сканирующая калориметрия; методика выявления и учета: активности рибосомных генов спутничных нитей акроцентрических хроматид - ЯОР; С-гетерохроматина; сестринских хроматидных обменов (СХО).

Результаты показали, что при старении пептидные биорегуляторы: 1) вызывают раскручивание - дегетерохроматинизацию общего гетерохроматина, конститутивного (прицентромерного, теломерного и ядрышкообразующих областей - ЯОР) и факультативного гетерохроматина; 2) индуцируют повышение уровня СХО, регистрируемых в теломерном гетерохроматине (дегетерохроматинизация) и снижают уровень СХО в медиальных областях хромосомных плеч (гетерохроматинизация); 3) каждый пептидный биорегулятор селективно дегетерохроматинизирует определенный специфический участок хромосом, высвобождая неактивные (когда-то активные) гены, что, по-видимому, может способствовать целенаправленному лечению болезней старения.

Предлагаемый генетический механизм, ответственный за ремоделирование конститутивного и факультативного гетерохроматина, подчеркивает значимость внешних и внутренних факторов в развитии заболеваний и может привести к разработке стратегии терапевтического лечения старческой патологии.

რეზიუმე

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„ადამიანის გენომის“ პროექტის დასრულების შემდეგ თანამედროვე გენეტიკის სტრატეგიულმა მიმართულებამ ფუნქციური გენომიკისაკენ გადაინაცვლა, რაც დნმ-ის არამაკოდირებელი უბნების ფუნქციების კვლევასაც გულისხმობს. ეს არამაკოდირებელი უბნები ჰეტეროქრომატინშია ლოკალიზებული. ჰეტეროქრომატინის ფუნქციები მნიშვნელოვანწილად გაურკვეველი რჩება.

შესწავლილია სინთეზური პეპტიდური ბიორეგულატორების (ტეტრაპეპტიდების Ala-Glu-Asp-Gly; Lys-Glu-Asp-Ala; Ala-Glu-Asp-Pro და დიპეპტიდის Lys-Glu) გავლენა ზოგად ჰეტეროქრომატინზე, კონსტიტუციურ (სტრუქტურულ) და ფაკულტატურ ჰეტეროქრომატინზე 75-88 და 20-40 წლის ინდივიდთა კულტივირებულ ლიმფოციტებში.

გამოყენებულია მოლეკულურ-ციტოგენეტიკური მეთოდები - დიფერენციული მასკანირებელი კალორიმეტრია; აკროცენტრულ ქრომოსომათა აქტიური რიბოსომული გენების სიხშირის დადგენა; C -ჰეტეროქრომატინის; შვილეულ ქრომატიდთა გაცვლების (შქგ) აღრიცხვის მეთოდები.

შედეგებმა აჩვენა,რომ დაბერებისას პეპტიდური ბიორეგულატორები: 1. იწვევენ ზოგადი ჰეტეროქრომატინის,კონსტიტუციური (პერიცენტრომერული,ტელომერული და ბირთვაკწარმომქმნელი რაიონების - ბწრ) და ფაკულტატური ჰეტეროქრომატინის გაშლას - დეჰეტეროქრომატინიზაციას; 2. ინდუცირებენ ქრომოსომათა ტელომერულ ჰეტეროქრომატინში რეგისტრირებული შქგ-ს დონის მატებას (დეჰეტეროქრომატინიზაცია) და აქვეითებენ შქგ-ს დონეს ქრომოსომული მხრების მედიალურ უბნებში (ჰეტეროქრომატინიზაცია); 3. თითოეული პეპტიდური ბიორეგულატორი სელექციურად ახდენს რა ქრომოსომის სპეციფიკური უბნის დეჰეტოქრომატინიზაციას და ათავისუფლებს არააქტიურ (ოდესღაც აქტიურად მოფუნქციე) გენებს,რამაც, როგორც ჩანს, შეიძლება ხელი შეუწყოს სიბერის ავადმყოფობათა მიზანმიმართულ მკურნალობას.

წარმოდგენილი გენეტიკური მექანიზმი, რომელიც პასუხისმგებელია კონსტიტუციური და ფაკულტატური ჰეტეროქრომატინის რემოდელირებაზე, ხაზს უსვამს დაავადებათა განვითარებაში გარეგანი და შინაგანი ფაქტორების მნიშვნელობას, და შეიძლება საფუძვლად დაედოს სიბერის პათოლოგიათა თერაპიული მკურნალობის სტრატეგიის შემუშავებას.

EPINEURIAL SUTURES, POLYETHYLENE GLYCOL HYDROGEL AND FIBRIN GLUE IN THE SCIATIC NERVE REPAIR IN RATS: FUNCTIONAL AND MORPHOLOGICAL ASSESSMENTS IN EXPERIMENT

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Mechanical damage to the peripheral nerve is a fairly common type of injury, which is characterized by a complex of long-term neurological disorders [2,4,10,11,19,28,33,38,41] and require significant financial costs [2,4,10,17,23,25,33,37,44]. Regeneration of the damaged nerve is a staged process and depends on a number of factors: the level and extent of damage, time from damage and microsurgical restoration, the method of microsurgery, revascularization [9]. The search for new and effective microsurgical techniques in the restoration of peripheral nerves is not complete.

The basic technical method of restoring the spatial integrity of the injured nerve is neuroraphy [14,16,31] – suturing the ends of the nerve "end-to-end" through epi- or perineurium with a biocompatible monofilament. The disadvantages of the method are time and financia cost, high manual qualification requirements for the surgeon, as well as the persistence of xenogenic suture material and incomplete spatial isolation of the injured area – additional triggers of local inflammatory reactions [3,13,29], which generally limit and slow down the regenerative growth of nerve fibers. All this motivates the development of sutureless sealed coaptation – adhesive, laser, photochemical [3,7,13-15,22,29,40,43,45,47], nanocomposite [18] or electrowelded [34].

The listed types of direct connection of nerve stumps, first of all, epineural suture (ES), are used in cases of easy, tension-free coaptation of nerve ends; otherwise recovery requires a graft [26]. The efficienc of regeneration and functional recovery is determined by the level of regeneration of nerve fibers through the sutured area, and if there are several such areas, as in the case of a graft, the number of regenerating nerve fibers in the distal nerve decreases. Grinsell D. and Keating C.P. note that at the level of one suture zone loses about 50% of nerve fibers, and after two suture areas - 75% [20].

The efficienc of functional recovery of the limb is influenced by both the level of nerve regeneration and the state of denervated muscles during reinnervation, such as malnutrition, fibrotic changes. The question arises of improving nerve regeneration by neuroraphy with innovative biodegradable polymers that would ensure the adhesion of the nerve ends and sufficien strength of this connection. The synthetic and biodegradable substances currently used in such way have partially realized this potential. Prospective data are available on the use of adhesives based on polyethylene glycol hydrogel (PEG) and fibrin glue (FG) [39]. The advantages of adhesives are ease of use, safety, less trauma to the nerve endings compared to ES, lower connective tissue density at the level of coaptation. However, there are concerns about the strength of connection of the nerve ends, so several ESs are still used to avoid "failure" of the suture [24]. Also, PEG and FG should not interfere with the regeneration of nerve fibers in the distal end of the nerve. Thus, FG is considered as an alternative to the microenvironment in conduits [12,32,35]. There is evidence for longer biodegradation of PEG in the damaged nerve and its better adhesion and strength compared to FG [30,42]. That is why a comparative analysis of the effectiveness of damaged nerve regeneration after different methods of neuroraphy is useful for neurosurgical practice.

The aim of the study was to evaluate the effectiveness of sciatic nerve regeneration after neuroraphy by ES, PEG and FG.

Material and methods. *The animal model.* The study was carried out with 30 white not purebred male rats (250±25 g, 5-6 months of age). Rats were randomly selected into the experimental groups:

Group № 1. Control – intact rats;

Group № 2. Shame-operated – a linear skin incision on the lateral surface of the femur was performed, the left sciatic nerve was isolated and mobilized. This was followed by layer-by-layer restoration of soft tissue integrity without nerve manipulation;

Group № 3. The complete transection (CT) of the sciatic nerve – the actions, as in the group № 2 with the additional complete transection of the sciatic nerve, the endings of the nerve were not connected, but remained freely in the wound. This was followed by layer-by-layer restoration of soft tissue integrity without nerve manipulation;

Group № 4. Epineural sutures (ES) – the actions, as in group № 2 with an additional complete transection of the sciatic nerve and its subsequent fixation end-to-end by epineurial neuroraphy with the atraumatic needle (4-6 epineurial sutures with a polyamide thread № 10/0);

Group № 5. Polyethylene glycol (PEG) – DuraSeal hydrogel – the actions as in group № 2 with an additional complete cross-section of the sciatic nerve and its subsequent fixation with use of hydrogel DuraSeal®, (Covidien LLC, USA) and 2 "fixating sutures"

Group № 6. Fibrin glue (FG) – Tisseel glue – the actions, as in group № 2 with an additional complete transection of the sciatic nerve and its subsequent fixation with Tisseel® fibrin glue and 2 "fixating sutures"

The surgery was performed under general anesthesia (xylazine 15 mg/kg and ketamine 70 mg/kg, intraperitoneally), according to the rules of asepsis and antiseptics. An access to the sciatic nerve in group 3 was performed as follows: an animal

was placed in a standard physiological position with its belly down, skin in the area of middle third of lateral surface of left thigh was shaved, treated with solution of povidone-iodine (Betadin, "EGIS", Hungary), dissected along the line of the most superficial location of the external femur surface, the area of attachment of both tendons of the biceps femoris to the femur was visualized, in this zone a linear section along the bone was performed; the muscle was allocated in the middle. The trunk of the sciatic nerve was visualized and opened at the interval from the exit from the pelvic cavity to the branching into the main branches. In animals of groups 3, 4, 5 and 6 at the middle of this site, the nerve was transected with microscissors.

In Group 4 animals, traditional epineurial neurorrhaphia with sutures was performed (Fig. 1). The left sciatic nerve in the middle third of the hip was crossed with microscissors. Microsurgical suturing was carried out after sciatic nerve transection with monofilament atraumatic thread № 10.0 in the amount of 4-6 until the fascicles were matched satisfactorily.

In the animals of group 5 and 6 after isolation and nerve transection, two epineurial sutures were applied with an atraumatic thread № 10.0 at the distance of 180^0 from each other.

In the group of animals № 5 after two fixation sutures were made Tisseel fibrin adhesive solution was applied to the nerve ending connection site, using the Duo Syringe System. The junction of the endings of the crossed nerve were covered with a thin layer of fibrin adhesive solution

In the 6th group of animals, after two fixation sutures were applied, a DuraSeal solution (5 ml Kit) was applied to the junction of the nerve endings. The system was prepared for the use according to instructions from the manufacturer. After the preparation of the system, gel was applied in a thin layer to the connected nerve site.

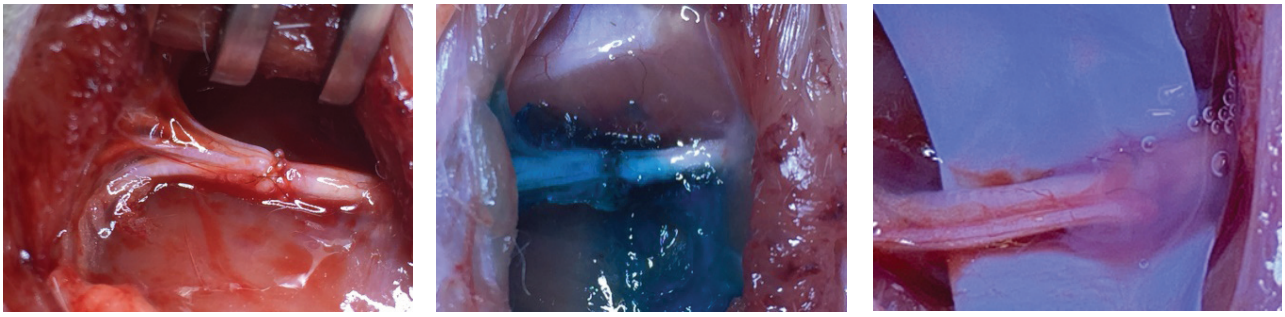
After the surgery and careful hemostasis in groups 2-6 layer-by-layer suturing of a postoperative wound was carried out with the certified atraumatic needle with a monofilament polyamide thread 4/0. In order to prevent infectious complications, benzyl penicillin solution in the dose of 1 mln u/1 kg body weight was administered to the posterior cervical site. For anti-inflammat - ry and anti-edema therapy, dexamethasone solution of 6 mg/kg body weight was administered intraperitoneally.

The Sciatic Functional Index (SFI). The SFI is aimed at quantitative assessment of the effects of the damaged sciatic nerve in rats. SFI quantifies functional deficits in animals by analyzing the trace change after injury. To do this, the limbs of rats were labeled with a dye (fucorcin) and rats were sent to the test track. Rat limb fingerprints were collected, the length between the limb fingers was measured and converted into quantitative values by the formula as described in the method [46].

Electroneuromyographic studies. Animals were anesthetized (intraperitoneal administration of a mixture of xylazine hydrochloride 15 mg/kg and ketamine hydrochloride 70 mg/kg) and fixed on the operating table belly down. A ground electrode (metallized tape soaked in 0.9% sodium chloride solution, 20 mm wide, 100 mm long) was fixed along the tail, and the sciatic nerve was isolated from the pelvic outlet till its branches, clearing the operating field with saline. The nerve was covered with a platinum hook-like bipolar electrode (monopolar diameter – 0.22 mm, distance between monopolars – 5,5 mm. The stimulating current was generated by a digital electroneuromyograph "Neuro-MVP-Micro" (LLC "NEUROSOFT", Russia), applied in pulse mode (pulse duration - 5 ms) with a frequency of 0.2 Hz (1 pulse for 5 sec) and a step of increasing the current at 1 mA. The excitation was recorded by the indicated electroneuromyograph using a concentric needle electrode (length - 25 mm, diameter - 0.3 mm, withdrawal area - 0.015 mm^2) at the motor point of the calf muscle. The distance between the stimulating and recording electrodes was ~ 25 mm. Analysis of neuromuscular function was assessed by ENMG parameters: M-response amplitude (AmV), latent M-response period (ms), excitation conduction velocity (mm/ms). For analysis only the parameters of the maximum M-response amplitude were used, which were obtained in most cases - at a stimulating current of 3 mA.

Histological and morphometric analysis. Distal sciatic nerve was fixed in 2.5% solution of glutaraldehyde in phosphate buffer with 1% osmium tetrachloride, dehydrated in increasing concentrations of ethanol and acetone. The tissue samples we embedded in the Epone-Araldite mixture. To get the ultrathin slices, we applied an ultratome (Reihart). The semi-thin sections were stained with toluidine blue, and then were stadied under a light microscope (Olympus BX 51) for histological and morphometrical examination. For morphometric examination, Carl Zeiss software (AxioVision SE64 Rel.4.9.1) and a camera attachment were used. Sciatic nerve samples for each rat were examined at high (×1000) magnification. The mean numerical density of the myelinated axons was estimated in photo (216×138 μm, average 0.03 mm^2), amount of sampling photo are 10-15 (2/3-3/4 of cros-section of nerve). The mean diameter (μm) of the myelinated axons was estimated by average of large and small diameters per individual fibe .

Data processing is carried out using the computer program of Origin v.9.0. The validity of the differences between the comparison groups was determined by Kruskal-Wallis H test. Diffe - ences between groups were considered statistically significant at $P<0.05$.



a b c

Fig. 1. Neuroraphy of the sciatic nerve of rats: a) sciatic nerve after ES; b) sciatic nerve after PEG (blue color); c) sciatic nerve after FG (white color)

All experimental procedures were conducted according of current standards of bioethics (EU Directive 2010/63/EU "on the protection of animals used for scientific purposes" (1986), European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (1986), Law of Ukraine of February 21, 2006 No. 3447-IV "About protection of animals against ill treatment" (2006)). The protocol of the study was approved by the bioethical commission of Bogomolets National Medical University (protocol 113).

Results and discussion. We analyzed the functional state of the limb of rats during the experiment with the use of SFI (Fig. 2). At 2 weeks after neuroraphy, a statistically significant higher SFI was found in the group with ES and PEG (P <0.05). At 3 and 4 weeks, SFI increased in all three groups (P <0.05). At 4 weeks, SFI values in the FG group were significantly lower compared to ES and PEG.

The results of electroneuromyography are shown in Fig. 3 and Table 1. It was was found significantly smaller amplitude of the M-response of the skeletal muscles of the shin in all three groups with neuroraphy. The amplitude of the M-response in the group with FG was smaller compared to the ES-group (P <0,05); there was no statistically significant difference between the ES and PEG groups. In the ES-group, the latency period of registration of the M-response was significantl longer (0.85 ± 0.05 ms vs 0.62 ± 0.04 in shame-operated rats). The latency period in the PEG- and FG-group approached to the control values (within the statistical error of control- to ES-group). The recorded excitation conduction velocity was significantly lower in the ES-group compared to control and Sham-operated rats by 25.1% and 31.1% (P <0.05) respectively. The excitation conduction velocity in the PEG- and FG-group is within the statistical error of the control and ES-group. The tendency in increase of the M-response in the PEG- and FG-group (except the amplitude in the FG-group) may indicate a more efficien reinnervation of skeletal muscles by regenerated nerve fibers from the damaged sciatic nerve. Statistically lower M-response rates in the ES-group indicate delayed (extended, prolonged) muscle reinnervation after neuroraphy compared to PEG- and FG-group.

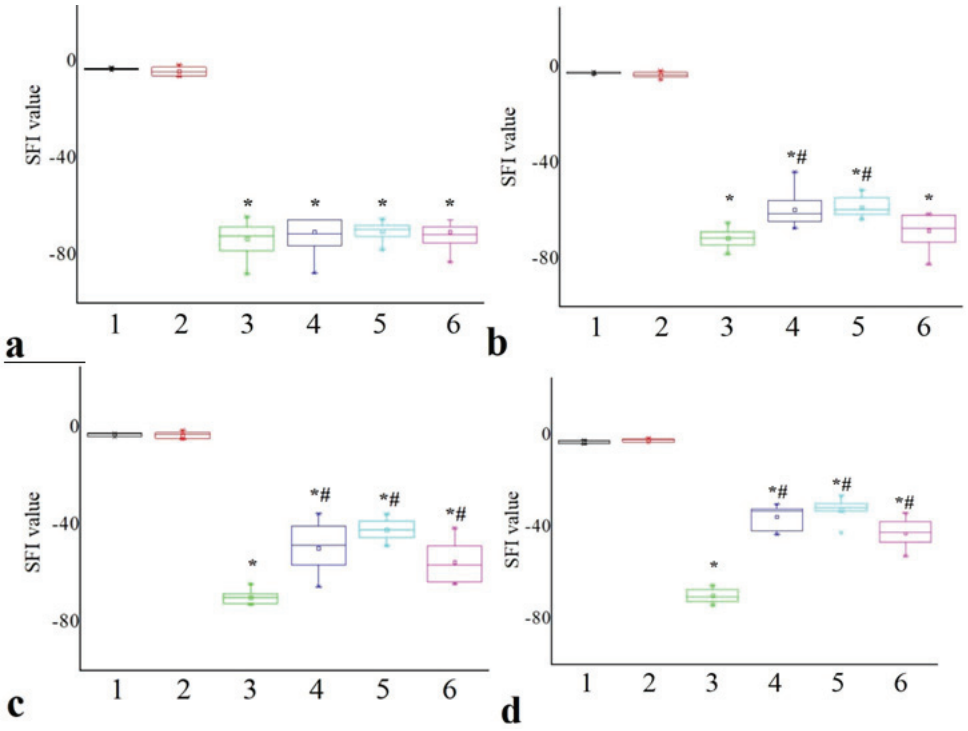


*Fig. 2. Charts of changes in SFI in rats after ES, PEG and FG (Mean±SD): a – 1 week; b – 2 weeks; c – 3 weeks; d – 4 weeks; on the abscissa: 1 – control; 2 – shame-operated group; 3 – neurotomy; 4 – ES; 5 – PEG; 6 – FG; * P < 0.05 in comparison with the control and shame-operated group; # P < 0.05 in comparison with the neurotomy*

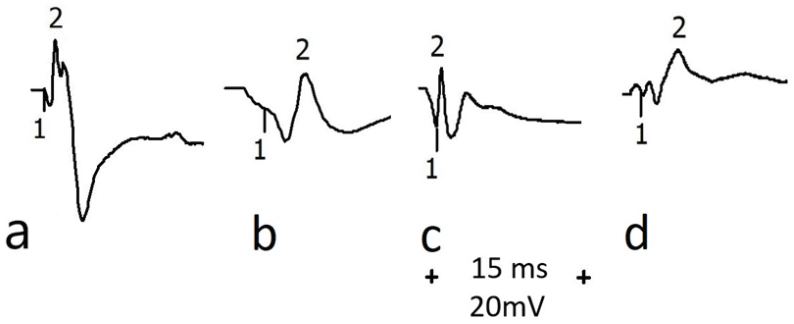


Fig. 3. Myograms recorded in rats on the 30-th day after neuroraphy: a – shame-operated group; b – ES; c – PEG; d – FG; 1 - primary-positive peak; 2 - positive peak

Table 1. Parameters of electroneuromyography in rats after sciatic nerve neuroraphy on the 30-th day (Mean±SEM)

Group	Amplitude of negative-positive peak, mV	Latency period, ms	Excitation conduction velocity, mm/ms
Control	19.3±0.95	0.68±0.02	40,9±1,61
Shame-operated	19.1±1.78	0.62±0.04	44,4±3,42
ES	6.67±1.19*	0.85±0.05@	30,6±1,40*
PEG	7.28±0.75*	0.76±0.06	37,9±2,94
FG	5.1±0.29*#	0.76±0.02	33,9±1,09

** - P<0.05 compared to the the control and shame-operated group;*
@ - P<0.05 compared to the the control and shame-operated group; # - P<0.05 compared to the the PEG

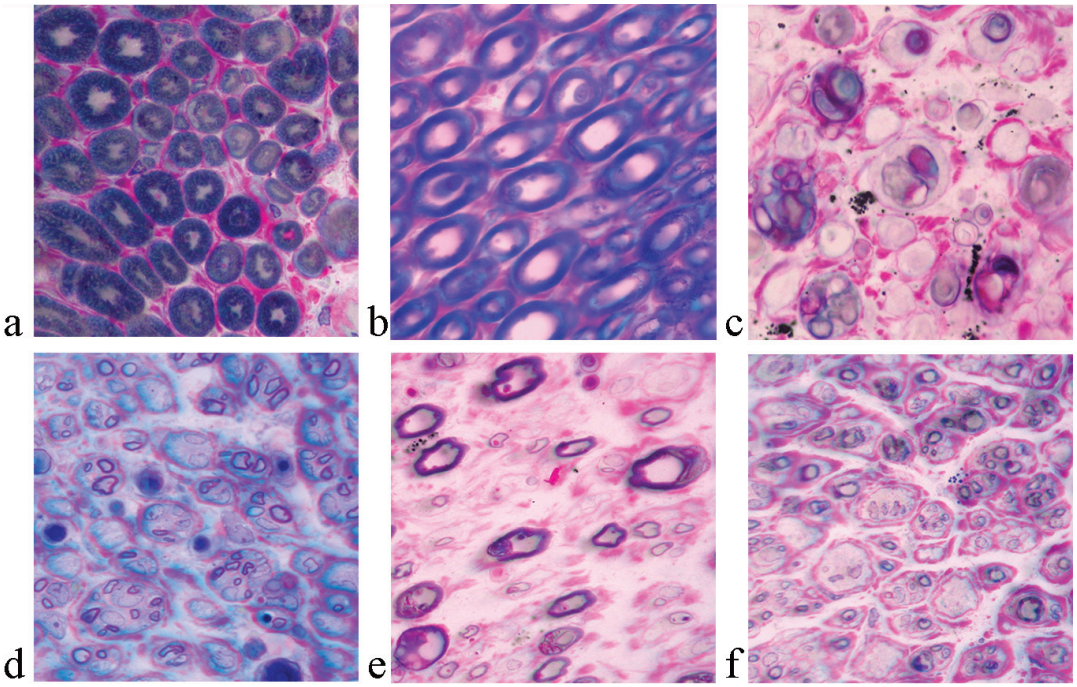


Fig. 4. Transverse section of a rat sciatic nerve stained by M.A. Hayat method: a – control; b – shame-operated group; c – neurotomy; d – ES; e – PEG; f – FG. Magnification ×1000

On the 30th day after neuroraphy, an analysis of the regeneration of myelin nerve fibers in the distal segment of the sciatic nerve was performed. Fig. 4 illustrates transverse half-thin sections of the sciatic nerves of the comparison groups. After complete neurotomy without neuroraphy, spontaneous regeneration was absent, so in the atrophically altered distal segment of the nerve the data were not analyzed (in table 2 presented as not analyzed, NA). According to the results of research in all cases after neuroraphy there was a regeneration of nerve fibers through the area of the nerve coaptation. Some tendencies between comparison groups were revealed. Thus, in PEG-group regeneration of «thick» myelin nerve fibers took place (number of nerve fibers by 25.9%, P <0.05; fiber diameter by 36.9%, P <0.05), and in FG-group regeneration of «thin» nerve fibers took place to a greater extent (number of nerve fibers by 38.3%, P <0.05). Morphometric analysis (Table 2) showed a significantly greater number of myelin nerve fibers in the distal nerve end in the PEG- and FG-group vs ES-group, and PEG promoted the regeneration of larger fibers (with a thicker myelin sheath). This indicates an acceleration of remyelination of axial cylinders on the 30th day after neuroraphy with the use of PEG.

Table 2. Morphometric data of myelin nerve fibers in the distal segment of the sciatic nerve on the 30th day (Mean±SEM)

Group	Number of myelinated nerve fibers, in test-zone	Diameter of myelinated nerve fibers, µm
Control	200.0±13.1	15.28±0.36
Shame-operated	197.4±10.7	15.81±0.35
CT	NA	NA
ES	38.5±2.4*	4.82±0.05*
PEG	48.5±2.7*^	8.58±0.18*^
FG	56.8±4.3*^	5.23±0.06*

** - P<0.05 compared to the control and shame-operated group; ^ - P<0.05 compared to the ES;*
NA – not analyzed (regeneration is absent)

This article aims to investigate the effectiveness of sciatic nerve regeneration in neuroraphy with use of epineural suture and connection with use of adhesives. There are concerns that PEG and FG are not strong enough to connect the nerve endings. This is confirmed by experimental data of some authors. Thus, the recovery of the nerve after the application of FG by the level of strength was equal to the recovery with the use of sutures only after 2-4 weeks [42]. Due to concerns about the strength of coaptation of the nerve ends, several sutures are still used, which increases the strength of the adhesive connection and reduces nerve injury due to fewer sutures.

Therefore, its use in clinical practice is limited only as an additional method in microsurgical suture reconstruction. In our own experiments, we followed the same algorithm. We first formed 2 fixating sutures and then applied PEG or FG, while the "classic" version of neuroraphy was the application of 4-6 epineural sutures. Analysis of the effectiveness of the recovery process included evaluation and comparison of functional and morphological data. The summarizing analysis indicates that PEG was significantly better at promoting functional recovery, both in terms of SFI (acceleration of limb locomotor function) and in terms of skeletal muscle M-response (latency response period and excitation conduction velocity). Compared with ES and PEG, the use of FG had less significant parameters compared to PEG. The study of cross sections of the sciatic nerve allowed to detect and quantify the regeneration rate of myelin nerve fibers, which explains the results of the M-response. Statistical analysis indicates a positive effect of PEG and FG on nerve regeneration, although significantly greater remyelination (analysis based on fiber diameter) was confirmed only in the group with PEG, which explains the faster functional recovery of the limb.

The data obtained by us confirm the experimental results of other authors [39, 40, 42], expend and clarify them. There are several views on the effect of PEG and FG on nerve regeneration: the direct effect of PEG and FG, the strength of the nerve connection, the state of the paraneural environment. Previously, it was hypothesized that PEG as a chemical fusogen could cause cell membranes to fuse (as used in vitro to fuse cells, create a hybrid cell line), in this case – a crossed axon, if PEG was applied in a short time period, and even were obtained some results [6]. But the analysis of the hypothesis, the evidential part of the results did not stand up to criticism, primarily due to the axial cylinders of the distal segment, which were "lost", are subjects to Waller's degeneration, which eliminates any possibility of axon fusion [8].

Although some authors still consider these theoretical issues [36]. Ovoids of degeneration we still have registered on the 30th day and the time of their elimination in the nerve is a separate factor that affects the recovery, because they are the products of destruction of damaged nerve fibers, which delay the tempo of regeneration. We did not analyze the elimination of ovoids, because we believe that the relative level of regeneration of nerve fibers is the main indicator of the effectiveness of recovery. According to this algorithm, the use of PEG gave better results than FG.

The direct action of FG is controversial. Thus, fibrin can inhibit cell migration and germination of nerve fibers [1], and at the same time can be used as an element of the extracellular matrix for adhesion and elongation of axons [27]. Another factor is the strength of the connection between the nerve endings. In a study [30], nerve ruptures at the level of coaptation were greater (more frequent) after nerve repair via FG, but not after sutures and PEG. Therefore, own experimental data and data of other authors [24, 30, 36] indicate better efficienc of PEG application in comparison with FG based on parameters of regeneration of nerve fibers, functional parameters or biomechanical characteristics. Although Koulaxouzidis G et al. [27] did not note diffe - ences in coaptation and nerve rupture between ES and FG. In this case, FG equally covers the nerve for up to 6 weeks [5], while in our own studies we did not register FG at the 4th week. We also hypothesize that PEG creates a temporary limiting biodegradable barrier around the damaged nerve from the paraneural environment, preventing scar formation after injury. The results of Isaacs J. et al. partially confirm this: the thickness of the perineural scarring tissue in the longitudinal projection of the nerves at the coaptation level was smaller after PEG vs FG [24]. In the same context, FG forms a fibrin capsule around the conduits, stimulates the infiltration of scar tissue, which prevents nerve regeneration, and promotes nerve regeneration in non-porous conduits [5]. Therefore, PEG in the form of a hydrogel is a more promising tool in microsurgical repair of damaged nerves as an adhesive, which promotes faster nerve regeneration, reinnervation of denervated muscles and functional recovery of the limb.

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SUMMARY

EPINEURIAL SUTURES, POLYETHYLENE GLYCOL HYDROGEL AND FIBRIN GLUE IN THE SCIATIC NERVE REPAIR IN RATS: FUNCTIONAL AND MORPHOLOGICAL ASSESSMENTS IN EXPERIMENT

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Mechanical damage to the peripheral nerve is a fairly common type of injury, which is characterized by a complex of long-term neurological disorders and require significant fina - cial costs. The aim of this work is to evaluate the efficienc of sciatic nerve (SN) regeneration after neuroraphy using epineural suture (ES), polyethylene glycol hydrogel (PEG), and fibrin glue (FG). The studies were carried out on 30 white outbred male rats, which were divided into six experimental groups: Group №1: intact rats; Group №2: Sham operated; Group №3: complete transection of the SN; Group №4: nerve repair with ES; Group №5: nerve repair with PEG; Group №6: nerve repair with FG. Functional recovery was assessed at 1, 2, 3, 4 postoperative weeks using a walking-track analysis with subsequent determination of the sciatic nerve functional index (SFI). At 4 weeks, electroneuromyography, histological and morphometric analyzes were performed. The combined analysis indicated that PEG significantly improved functional recovery, both in the SFI index and in the skeletal muscle M-response. Compared to ES and PEG, the use of FG was reflected in a lower significance of the indicators compared to PEG. Statistical analysis indicates a positive effect of PEG and FG on nerve regeneration, although significantly greater remyelination (analysis based on fiber diameter) was confirmed only in the PEG group, which explains the faster functional recovery of the limb. PEG in the form of a hydrogel is a more promising agent in microsurgical restoration of damaged nerves as an adhesive, it promotes rapid nerve regeneration, denervated muscle re-innervation and functional limb recovery.

Keywords: sciatic nerve, repair, epineural sutures, polyethylene glycol hydrogel, fibrin glue, functional outcome

РЕЗЮМЕ

ЭПИНЕВРАЛЬНЫЙ ШОВ, ПОЛИЭТИЛЕНГЛИКОЛЬ ГИДРОГЕЛЬ И ФИБРИНОВЫЙ КЛЕЙ В ВОССТАНОВЛЕНИИ СЕДАЛИЩНОГО НЕРВА: ФУНКЦИОНАЛЬНАЯ И МОРФОЛОГИЧЕСКАЯ ОЦЕНКА В ЭКСПЕРИМЕНТЕ

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Механическое повреждение периферического нерва - весьма частый вид травмы, который характеризуется комплексом длительных неврологических расстройств и обусловливает значительные финансовые затраты.

Цель исследования - оценка эффективности регенерации седалищного нерва после нейрорафии с помощью эпиневрального шва, полиэтилен гликоля гидрогеля и фибринового клея. Исследования проводились на 30 белых беспородных самцах крыс, которые разделены на шесть экспериментальных групп: группа №1 - интактные крысы; группа №2 - ложно-оперированные; группа №3 - полное пересечение седалищного нерва (СН); шруппа №4 - соединение концов СН с помощью эпиневрального шва (ЭШ); группа №5 - соединение концов СН с помощью полиэтилен гликоля гидрогеля (ПГГ); группа №6 - соединение концов СН с помощью фибринового клея (ФК). Функциональное восстановление оценивалось в конце I, II, III, IV недели после операции с помощью тест-ходов на дорожке с последующим определением функционального индекса седалищного нерва (ИСН). На IV неделе проводили электронейромиографию, гистологический и морфометрический анализы. Обобщающий анализ указывает, что ПГГ достоверно лучше способствовал функциональному восстановлению, как по ИСН, так и М-ответу скелетных мышц. В сравнении с ЭШ и ПГГ, применение ФК отразилось в меньшей значимости показателей относительно ПГГ. Статистический анализ указывает на положительное действие ПГГ и ФК на регенерацию нерва, хотя достоверно большая ремиелинизация (анализ на основе диаметра волокон) подтверждена только в группе с ПГГ, что объясняет более быстрое функциональное восстановление конечности. ПГГ в форме гидрогеля является более перспективным средством в микрохирургическом восстановлении поврежденных нервов в качестве клея, способствует быстрой регенерации нерва, реинервации денервированных мышц и функциональному восстановлению конечности.

რეზიუმე

ეპინევრული ნაკერი, პოლიეთილენგლიკოლ-ჰიდროგელი და ფიბრინული წებო საჯდომი ნერვის აღდგენაში: ფუნქციური და მორფოლოგიური შეფასება ექსპერიმენტში

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პერიფერიული ნერვის მექანიკური დაზიანება ტრავმის საკმაოდ ხშირი სახეა, რომელიც ხანგრძლივი ნევროლოგიური დარღვევებით ხასიათდება და მნიშვნელოვან ფინანსურ დანახარჯს განაპირობებს.

კვლევის მიზანს წარმოადგენდა საჯდომი ნერვის რეგენერაციის ეფექტურობის შეფასება ნეირორაფიის შემდეგ ეპინევრული ნაკერის, პოლიეთილენგლიკოლ-ჰიდროგელის და ფიბრინული წებოს გამოყენების პირობებში. კვლევა ჩატარდა 30 თეთრ უჯიშო მამრ ვირთაგვაზე, რომლებიც დაიყო ექვს ექსპერიმენტულ ჯგუფად: ჯგუფი I – ინტაქტური ვირთაგვები; ჯგუფი II – ცრუ-ნაოპერაციებთა ჯგუფი; III – საჯდომი ნერვის სრული გადაკვეთა; ჯგუფი IV – საჯდომი ნერვის ბოლოების დაკავშირება ეპინევრული ნაკერით; ჯგუფი V – საჯდომი ნერვის ბოლოების დაკავშირება პოლიეთილენგლიკოლ-ჰიდროგელით; ჯგუფი VI – საჯდომი ნერვის ბოლოების დაკავშირება ფიბრინული წებოთი.

ფუნქციური აღდგენა ფასდებოდა ოპერაციიდან I, II, III და IV კვირის ბოლოს სიარულის ტესტის

საშუალებით, საჯდომი ნერვის ფუნქციური ინდექსის შემდგომი განსაზღვრით. IV კვირას ტარდებოდა ელექტრონეირომიოგრაფია, ჰისტოლოგიური და მორფომეტრიული ანალიზები.

შედეგების განზოგადება მიუთითებს, რომ პოლიეთილენგლიკოლ-ჰიდროგელი მეტად უწყობს ხელს ფუნქციურ აღდგენას როგორც საჯდომი ნერვის ფუნქციური ინდექსის, ასევე, ჩონჩხის კუნთების მიოგრაფიული პასუხის მიხედვით. ეპინევრულ ნაკერთან და პოლიეთილენგლიკოლ-ჰიდროგელთან შედარებით, ფიბრინული წებოს გამოყენებამ განაპირობა მაჩვენებლების ნაკლები სიდიდე პოლიეთილენგლიკოლ-ჰიდროგელთან მიმართებით.

სტატისტიკური ანალიზი მიუთითებს პოლიეთილენგლიკოლ-ჰიდროგელის და ფიბრინული წებოს დადებით გავლენაზე ნერვის რეგენერაციაზე, თუმცა, სარწმუნოდ უფრო მაღალი რემიელინიზაცია (ბოჭკოთა დიამეტრის ანალიზის მიხედვით) დადასტურდა მხოლოდ პოლიეთილენგლიკოლ-ჰიდროგელის ჯგუფში, რითაც აიხსნება კიდურის უფრო სწრაფი ფუნქციური აღდგენა. დაზიანებული ნერვების მიკროქირურგიული აღდგენისას პოლიეთილენგლიკოლი ჰიდროგელის სახით წარმოადგენს უფრო პერსპექტულ საშუალებას, როგორც წებო, უწყობს რა ხელს ნერვის სწრაფ რეგენერაციას, დენერვირებული კუნთების რეინერვაციას და კიდურის ფუნქციურ აღდგენას.

PECULIARITIES OF ACTIVATION OF COMPENSATORY-ADAPTIVE PROCESSES IN ADULT RAT LIVER CAUSED BY UNILATERAL NEPHRECTOMY

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At the modern stage, the study of the mechanisms of compensatory-adaptive processes of separate as well as inter organs, has acquired special importance. The urgency of the problem is further enhanced by its social nature. Deep study of these mechanisms allows for the rational employment of such people after treatment. In this sense, special attention is given to organs such as the heart,liver and kidneys. Recently, two types of responses after acute organ failure have appeared to be shared in the liver, heart, and kidney: (i) surviving differentiated parenchymal cells undergo cell hypertrophy via polyploidization; and (ii) a population of progenitors, mostly identified as resident, more immature diploid parenchymal cells, self-renew and differentiate to replace lost cells [12]. Complex metabolic transformations, as well as detoxific tion and filtratio processes, as it is known, maintain the body's homeostasis [5]. A pathological condition that develops during liver damage and revealed in impaired kidney function, including acute renal failure, has been known for about 100 years as hepatorenal syndrome. Despite numerous treatments, a significant reduction in mortality has not been achieved to date [3,13,15-17].

Particular importance today is also attached to the study of compensatory mechanisms induced in response to increased functional load on the liver after various renal pathologies or resections. Latent hepatopathy caused by increased functional load on the liver in response to renal resection is revealed in experimental animals and patients. Thus, any changes in the functioning of these organs, including those caused by surgery, increase the risk of severe complications and inevitably lead to systemic disorders. Based the above, the urgency of the problem of inter organ compensatory mechanisms and the expediency of intensive research in this direction is clear [4].

Recent studies have found relatively little information that compensatory and adaptive growth of liver is not always accompanied by strictly regulated sequential regeneration processes such as proliferation, hypertrophy, and polyploidy. For example, it has been shown that 4 days after the common bile duct ligation, ploidy of destructive liver parenchyma cells is increased [7]. Increasing of the degree of polyploidy was found under radiation and oxidative stress [10]. It has been established that, in the case of alimentary dyslipidemia, the mechanism of regeneration depends on the duration of use of the hepatogenic ration and the degree of damage [1]. Clinical trials have shown that after unilateral nephrectomy for any reason, patients need constant follow-up, since the changes that develop over the years in the remaining kidney primarily affect liver function [14]. For example, after unilateral nephrectomy decrease in urine output and glomerular filtration, which leads to the so-called latent hepatopathy is occur [2]. At the same time, it is not yet known, for example, which mechanism of adaptive growth is used by the liver in response to dysfunction resulting from unilateral nephrectomy.

Evaluation of changes in hepatocyte ploidy of white adult rats at different time from unilateral nephrectomy is the aim of the wo k.

Material and methods. *Experimental Animals and Model.*

Experiments were carried out on adult white rats(130-150 g). All laboratory animals have been housed in cages at room temperature (25°C), with free access to standard food and water chow and subjected to a 12 h light/dark cycle. Unilateral nephrectomy (resection of the right kidney) was performed under ether anesthesia.

Experimental groups

The animals were divided into 2 groups: 1. Control group - intact rats that underwent false surgery; 2. Experimental group - animals that underwent unilateral nephrectomy. liver and renal tissue (study material) was taken at 24 h, 48 h, 72 h, after Unilateral nephrectomy.

1 mg/kg of colchicine (Sigma, USA) was injected into the animals of both the control and the test groups for determination of the colchicine mitotic index per 1000 cells (‰).

Fixation and embedding in paraffin of liver tissue

Liver and renal tissue was fixed in formalin (4% solution ph 7.2-7.4 for 2 days). After fixation, the tissue sections were dehydratedby passing through in increasing concentration of alcohol baths (70%- 30 min, 80%- 30 min, 96%- 30 min). Then, tissues were placed in acetone three times for 20 min each, acetone-benzoyl (1:1) for 30 min, benzoyl three times for 20 min each. Placed in Paraffi wax (58-60 ºC), three changes, 1 hours each. Tissues were embedded into paraffi blocks. Tissues were sectioned by Leica microtome (thickness of sections -5µm) and stained using standard protocol of Hematoxylin and eozine (H&E) [8].Tissue samples were studied under the light microscope (Zeiss Primo Star, Germany).

Preparation of Schiff's reagent and smears staining

Hepatocytes smears were stained by Schiff reagent (Feulgen staining). Schiff s reagent was prepared as follows: 200ml of boiling, distilled water were poured on 1g of powdered basic fuchsin. After cooling to 50°C, the solution was filtered and 20ml of 1 N HCl was added, cooled to 25°C and 2g of $K_2S_20_5$ was added. Vacate overnight in a dark place. The bisulfite washing solution was composed of 10 ml 10% $K_2S_20_5$, 10 ml1 N HCl 100 ml of distilled water.

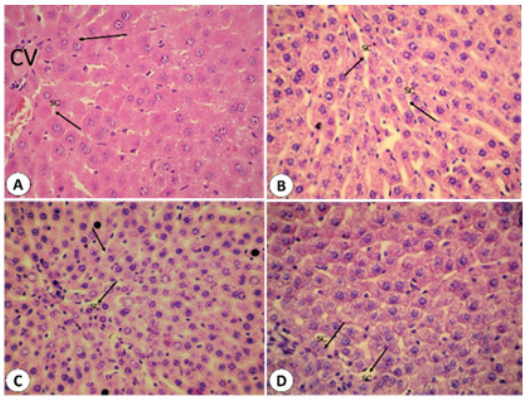
After fixation of methyl alcohol, the smear was fixed in 5% sulfosalicylic acid for 10 minutes, rinsed in distilled water and placed in solution (LiCl 9M + HCl 0.2M) for 20 minutes, rinsed in 0.01 M HCl; Placed in the dye (Schiff reagent) for 30 minutes-1 hour.Moved inbisulfite washing solution three times for 5 min each; rinsed in 0,01 M HCl; than alcohol baths (80°-5 min, 96°-5 min); Placed in xylol, two changes, 20 min each and mount in mounting media.

Conventional light microscope, ocular micrometer and stage micrometer were used for morphometry. The ocular micrometer was calibrated using a stage micrometer - the size of the divisions on the ocular micrometer was determined at the appropriate magnification. Immersion objective (X100) and H&E stained preparations were used for the measurement. For each structure were measured height and width, reseved numbers were multiplied and obtained the area. 300 cells were measured for each sample [6,11].

Nuclear DNA content was detected by using of computer software ImageJ 1.36 b.

Results and discussion. Polyploidy as shown is a common biological phenomenon, influences all levels of biological organization, from genes to cells to entire ecosystems Yet, polyploidy remains underexplored in many contexts, and its roles and impact in biological processes and across phylogeny are unclear [9].

Using the above methods, carried out a comparative assessment of changes in liver histoarchitectonics and proliferative activity in control and experimental animals (unilateral kidney resection). Fig. 1 shows intact rat liver (Fig.1 A,B,C,D) where the typical histoarchitectonics of adult rat liver is clearly visible: the classical lobular structure, the oval-shaped central vein (CV) located in the center of the lobule, liver plates radiated from the periphery, polygonal-shaped parenchymal cells - hepatocytes (both mono and binuclated) assembled into plates in one or two rows and sinusoidal capillaries located between them (Fig. 1A).



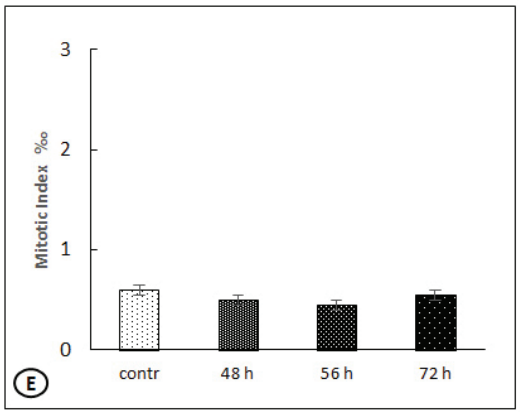
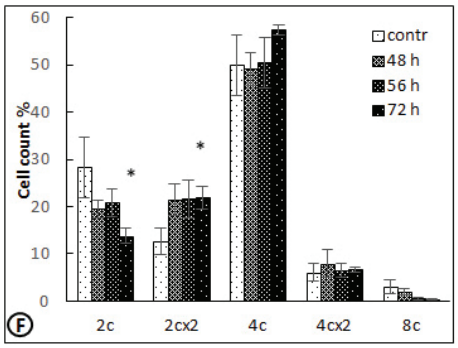


Table 1

Groups	Cell area (µm²)	Nucleus area (µm²)
Contr	259±2,7	35±1
48h	372±9*	54±3,5*
56h	360±9	53±2,4
72h	381±21	55±3,4



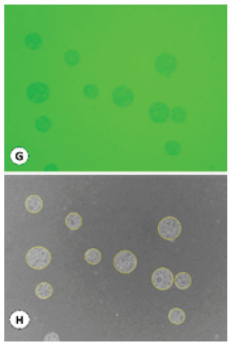
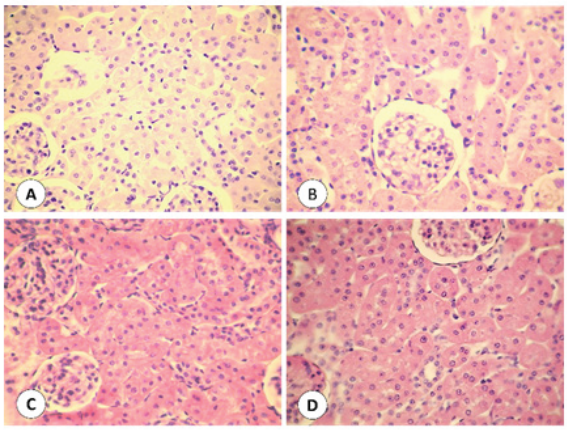


Fig. 1. A, B, C, D. Light microscope micrograph of the rat liver tissue. A - control. The photo shows the classic particle structure. In the particles we see: oval-shaped cavity – the central vein (CV) and sinusoids (SC); B - 48 hours after nephrectomy; C - 56 hours after nephrectomy; D - 72 hours after nephrectomy. The photos clearly show slightly enlarged sinusoids. E - Mitotic index change in hepatocytes at 48, 56 and 72 h after unilateral nephrectomy; Table 1 - results of measurement of liver tissue cells and nuclei areas; F - ploidy change in hepatocytes at 48, 56 and 72 h after unilateral nephrectomy. G - isolated hepatocytes stained with Feulgen reaction; H - Image in computer program Image J



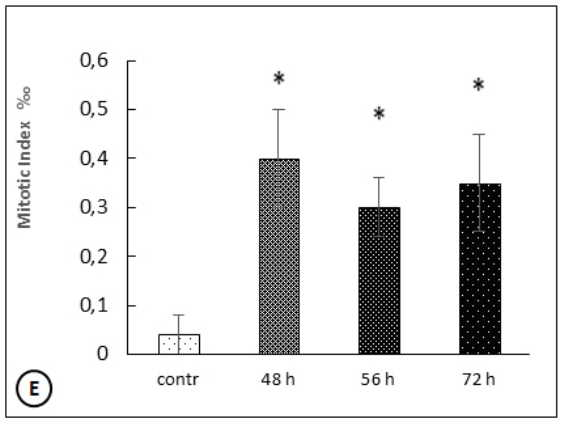
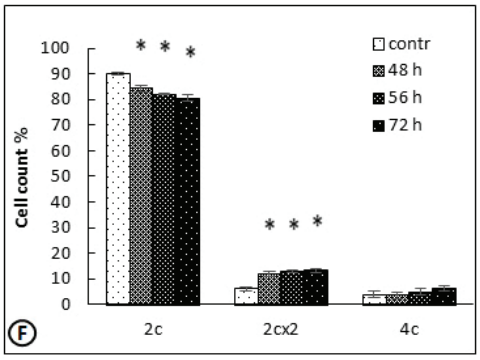


Table 2

Groups	Cell area (μm²)	Nucleus area (μm²)
Contr	112±4	29±1
48h	139±4*	35±1*
56h	170±2*	37±1
72h	182±11	39±2



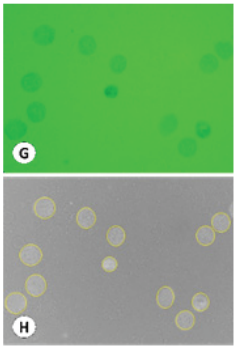


Fig. 2 A, B, C, D. Light microscope micrograph of the rat kidney tissue. A – control; B - 48 hours after nephrectomy; C - 56 hours after nephrectomy; D - 72 hours after nephrectomy; F - ploidy change in hepatocytes at 48, 56 and 72 h after unilateral nephrectomy. The photos clearly show the typical distribution of renal tubules and blood vessels in space; E - mitotic index change in kidney at 48, 56 and 72 h after unilateral nephrectomy; Table 2 - results of measurement of kidney tissue cells and nuclei areas; F - ploidy change in kidney at 48, 56 and 72 h after unilateral nephrectomy; G – isolated kidney cells stained with Feulgen reaction; H - image in computer program Image J

How does the hepatic architecture change after eremoval of the right kidney? Studies have shown that within 48 hours of unilateral nephrectomy the microscopic picture of the liver ischanged slightly . The radial structure of the organ is preserved (Fig. 1B). However, there is a change in the relationship between the sinusoids and the liver plates. In particular, slightly enlarged sinusoids (SC) are well visible. Nevertheless, the disruption of the typical structure of hepatocytes is not manifested in the liver tissue. Similar changes are observed at 56 and 72 hours after operation, with the expansion of sinusoids more pronounced at 72 hours (Fig. 1C,D). The results show that the effect of unilateral nephrectomy on rat liver histoarchitectonics is morphologically appears only in the changing of the spatial relationship of the sinusoids and liver plates within 72 hours.

Against the background of these changes, we have assessed the proliferative activity of liver parenchymal cells. It was found that unilateral nephrectomy did not change mitotic index of the liver in animals of experimental group during the first three days (48th, 56th and 72nd hours) (Fig. 1E).

At the same time, some structural changes were revealed after the morphometric analysis of hepatocytes and their nuclei. In particular, it was found that at 48 hours after unilateral nephrectomy, the areas of hepatocytes and their nuclei are increased compared to controls in the liver. These data remain unchanged at 56 h and 72 h after the operation (Fig.1, Table 1).

In cholestatic liver-induced by common bile duct ligation as well as in dyslipidemia, as already mentioned above, have been shown that Increased functional load at early stage initiates polyploidy in the liver (7, 1). Therefore, we have studied the changes in the quantitative ratio of hepatocytes with diffe - ent ploidy in the liver of animAals of control and experimental groups. It was found that in 48 hours after the operation the ratio of different ploidy hepatocytes did not statisticaly change compared to control. Also, no changes in the genome content of hepatocytes were observed at 56 h after surgery compared to intact animals. In particular, diploid (2c) and tetraploid (2cx2) cells were reducedstatistically significant, while the number of 4c, 4cx2, and 8c cells remained unchanged (Fig. 1F).

We also assessed the change in renal histoarchitectonics from unilateral nephrectomy on above dates. The micrographs presented in Figure 2 show the renal histoarchitectonics of the control rats. In particular, the typical distribution of renal tubules and blood vessels in the space and the structure of the distal and proximal tubules of the nephrons is well visible. In their lumens, renal epithelial cells with eucromatin nuclei and moderately active nuclei are well distinguished (Fig. 2A).

At 48 hours after unilateral nephrectomy, no visible changes are observed in renal histoarchitectonics, but it is important to note that the proliferative activity of nephrocytes increases very slightly but significantly (Fig. 2. B). Increased mitotic index is also apeare at 56 and 72 hours after nephrectomy

(Fig. 2 C, D, E), which may be associated with an increased functional load on the organ. Morphometric analysis of cells and nuclei in renal tissue revealed that at 48 hours after unilateral nephrectomy, the area of nephrocytes nephrocytes statistically increased in comparison with the control. The area of nephrocytes statistically increased also at 56 and 72 hours after surgery (Fig. 2, Table 2).

Quantitative analysis of DNA in isolated nephrocytes of animals of control and experimental group showed that number of diploid (2c) cells decreased and percentage of tetraploid (2cx2) cells increased statistically significantly at 48 h after unilateral nephrectomy compared to intact animals. The number of binucleited tetraploid cells also increased at 56 and 72 hours after the opration (Fig. 2 F).

From obtained results follow that the kidney responds to the functional load caused by unilateral nephrectomy by increasing the number of high ploydy cells. The fact that the number of polyploid cells in the kidney increases 24 hours earlier than in the liver may be explained by a more rapid increase in the functional load on the second kidney.

Conclusions. The results obtained by us show that in conditions of hepatopathy caused by unilateral nephrectomy, as in some other pathologies, in response to increased functional load, the liver prefer polyploydy from the inter-organ compensatory-adaptive mechanisms at the initial stage. After unilateral nephrectomy, in the second kidney of adult white rats, in the initial stage, an increase in the number of high-ploydy cells allows us to think that cell polyplodization is a preferred compensatory adaptative mechanism characteristic of parenchymal organs in response to increased functional load.

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SUMMARY

PECULIARITIES OF ACTIVATION OF COMPENSATORY-ADAPTIVE PROCESSES IN ADULT RAT LIVER CAUSED BY UNILATERAL NEPHRECTOMY

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In order to determine the general patterns of activation of the inter organ compensatory-adaptive processes, the peculiarities of activation of compensatory processes caused by unilateral nephrectomy in adult rat liver at the initial stage of hepatopathy (first three days after the operation) have been studied. In particular, it has been established that only small but visible abnormalities in the spatial relationship of sinusoids and hepatic plates are revealed morphologically in rat liver histology. The increasing of the functional load caused by changes in histoarchitecture, at these times, does not stimulate hepatocyte proliferation. At the same time, it is revealed that at the initial stage of hepatopathy caused by unilateral nephrectomy, preference is given to polyploidy from compensatory-adaptive processes charachterised to liver. In particular, it has been shown that liver responses mainly by quantitative increases in binucleated cells (2cx2) to the functional load induced by unilateral nephrectomy at an early stage.

Keywords: white rat, liver, unilateral nephrectomy, polyploidy.

РЕЗЮМЕ

ОСОБЕННОТИ АКТИВАЦИЙ КОМПЕНСАТОРНО-ПРИСПОСОБИТЕЛЬНЫХ ПРОЦЕССОВ ПРИ ОДНОСТОРОННЕЙ НЕФРЭКТОМИИ В ПЕЧНИ ВЗРОСЛЫХ КРЫС

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С целью определения общих закономерностей активации механизмов межорганных компенсаторно-приспособительных процессов, изучены особенности компенсаторных процессов в печени взрослых белых крыс на начальной стадии гепатопатии, вызванной односторонней нефрэктомией (первые три дня после операции). В частности, установлено, что морфологически в гистоархитектуре печени крысы выявляются лишь небольшие, но видимые изменения пространственного соотношения синусоид и печеночных протоков. В печени увеличение функциональной нагрузки, вызванное изменениями гистоархитектуры, в это время не стимулирует пролиферацию гепатоцитов. В то же время выявлено, что на начальной стадии гепатопатии, вызванной односторонней нефрэктомией, предпочтение отдается полиплоидии из компенсаторно-приспособительных процессов, характерных для печени. В частности, было показано, что реакция печени в основном выражается в количественном увеличении двуядерных клеток (2cx2) на функциональную нагрузку, вызванную на ранней стадии односторонней нефрэктомией.

რეზიუმე

ზრდასრული თეთრი ვირთაგვას ღვიძლში ცალმხრივი ნეფრექტომიით გამოწვეული კომპენსატორულ-ადაპტაციური პროცესების აქტივაციის თავისებურებები

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ივანე ჯავახიშვილის სახ. თბილისის უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ბიოლოგიის დეპარტამენტის მორფოლოგიის კათედრა, საქართველო

ორგანოთაშორისი კომპენსატორულ-შეგუებითი პროცესების მექანიზმების აქტივაციის ზოგადი კანონზომიერებების დადგენის მიზნით, შესწავლილია ცალმხრივი ნეფრექტომიით გამოწვეული ჰეპატოპათიის საწყის ეტაპზე (ოპერაციიდან პირველი სამი დღე) ზრდასრული თეთრი ვირთაგვების ღვიძლში კომპენსატორული პროცესების მიმდინარეობის თავისებურებები. კერძოდ, დადგენილია, რომ აღნიშნულ ვადებზე ვირთაგვას ღვიძლის ჰისტოარქიტექტონიკაში მორფოლოგიურად მხოლოდ სინუსოიდების და ღვიძლის ბაგირაკების სივრცითი ურთიერთობის მცირე, მაგრამ თვალსაჩინო დარღვევები ვლინდება. ღვიძლზე, ჰისტოარქიტექტონიკის ცვლილებებით გამოწვეული ფუნქციური დატვირთვის გაზრდა, აღნიშნულ ვადებზე, არ იწვევს ჰეპატოციტების პროლიფერაციის სტიმულაციას. ამავე დროს, გამოვლინდა, რომ ცალმხრივი ნეფრექტომიით გამოწვეული ჰეპატოპათიის საწყის ეტაპზე, ღვიძლისთვის დამახასიათებელ ორგანოთაშორისი კომპენსატორულ-შეგუებითი პროცესებიდან უპირატესობა პოლიპლოიდიზაციას ენიჭება. კერძოდ, ნაჩვენებია, რომ ცალმხრივი ნეფრექტომიით გამოწვეულ ფუნქციურ დატვირთვას ზრდასრული ვირთაგვას ღვიძლი საწყის ეტაპზე ძირითადად ორბირთვიანი უჯრედების (2cx2) რაოდენობრივი მატებით პასუხობს.

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CORRELATION OF BLOOD BIOCHEMICAL INDICATORS WITH THE LEVEL OF KNEE JOINT DAMAGE IN THE MODEL OF THE POSTTRAUMATIC OSTEOARTHRITIS

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Osteoarthritis is a chronic joint disease, which consists of dystrophic changes in the articular surface, alteration of the cartilage of the joint, damage of the meniscus and a subchondral bone [1]. The disease has a different etiology, is often the result of trauma and age-related changes and is characterized by an insufficien level of treatment effectiveness [2]. The role of vascular factor in the development of osteoarthritis is being considered. In addition to direct injury, there are two other factors that reduce the metabolic support of joint tissues during inflammation, namely insufficien oxygen delivery due to poor perfusion in the inflamed joint and subsequent peroxidation by forming proinfla - matory molecules, vascular and joint necrosis [3]. Therefore, the viability of the epiphyseal cartilage of the joint depends on the adequate blood supply to the surrounding vessels, and strongly affects the state of blood supply in the pathogenesis of osteochondrosis, osteoarthritis [4].

A perspective direction of regenerative medicine is the use of autologous cell therapies. Currently, several areas like this have begun to be used: the introduction of platelet-rich plasma (PRP), cells derived from aspirated bone marrow cells (BM) and

adipose tissue (AT) [5]. PRP is obtained as a product of blood plasmaphoresis, the concentration of platelets in which is significantly higher than the initial values in the blood (6×10^3-7×10^8 1/ml) [6,7]. The strategy of its application is explained by the trophic action of growth factors (PDGF, VEGF, FGF and others) released from platelet granules [8]. The possibility of introducing BM- and AT-derived mesenchymal cells is also being considered [9,10]. There is a discussion about the direct trophic action of these cell suspensions and PRP, some conclusions are speculative. We reckon that adipose tissue aspirate may be an alternative instead of using the red bone marrow cells and platelet plasma. In this study, we hypothesized that the introduction of bone marrow aspirate concentrate (BMAC) and mechanically homogenized adipose tissue (MHAT) cell suspensions and PRP into the knee joint helps to support articular cartilage in osteoarthritis, activates the regenerative processes in damaged tissues, which can be detected on the basis of histological studies of the knee joint and blood biochemical parameters.

In this work, we investigated the influence of BMAC and MHAT cell suspensions and PRP on changes of a knee joint and their correlation with biochemical indicators of blood.

Material and methods. The study was carried out on Chinchilla rabbits (n=25, weighing 3-4 kg). The research was performed in 2 stages. On the first stage, post-traumatic osteoarthritis (PTOA) was simulated in intact animals. Animals were observed for 30 days. On the second stage, cell suspensions were injected into the injured animals' knee joint. Animals were divided into 5 groups: group 1 – control group (n=4); group 2 - PTOA group (n=6); 3 – BMAC group (n=5); 4 – MHAT group (n=5); 5 – PRP group (n=5). In 45 days, the animals received blood from the jugular vein (animals were anesthetized with sodium thiopental, 60 mg/kg, ip), serum was taken for biochemical examination. Animals were anesthetized to a lethal dose. The knee joint was isolated for histological studies.

Model of post-traumatic osteoarthritis (PTOA). Rabbits under anesthesia were shaved at the level of the ankle joint. The knee joint capsule was accessed through the medial surface, the medial ligament was crossed. The central area of the articular surface of the tibia was mechanically damaged by circular rotations with a low-speed drive with a modified Ilizarov needle with soldering caused damage to the joint surface (speed 1000±5 rpm). The standard lesion area is 2.0×2.1 mm. The epiphyseal surface of the femur and the meniscus of the joint were left intact. The joint bag was sutured with suture material 3/0 "Prolene" ("Ethicon," Scotland). For additional damage to the joint capsule, its surface was thermally damaged by a coagulator. The area of thermal damage is 9.5-10.0 mm^2. The skin was sutured with material 3/0 "Prolene" ("Ethicon," Scotland) and irrigated with betadine ("Egis", Hungary).

Bone Marrow Aspirate Concentrate (BMAC). In intact rabbits, an autologous bone marrow aspiration of 2.0 ml was performed with a 10 ml diameter bone trocar and a 5 ml syringe from the rabbit's proximal thigh. Bone marrow aspirate with dextrose citrate (1:8) ACD-A (Baxter SA, USA/Belgium) was centrifuged for 16 minutes at 740g. Animals were administered 1.0 ml of BMAC.

Mechanically homogenized adipose tissue (MHAT). In intact rabbits, 1.0 cm^3 of adipose tissue was obtained from a large omentum. Adipose tissue was mechanically homogenized by passing 10 times through a 1 mm cannula (gentle method). The volume of injection into the joint is 1.0 ml.

Platelet rich plasma (PRP). To 10.0 ml of blood was added 1.0 ml of 3.8% sodium citrate and centrifuged at 400 g for 15 min (t=4°C). The platelet layer was removed (by cytological analysis $0.8\text{-}1.0\times10^6$ 1/ml). Donor blood was used as in similar studies [11,12].

Serum parameters were determined on μQuant spectrophotometers (Bio-Tek, USA). The method was used to determine the level of thiobarbituric acid-reactive substances (TBARS) [13], ceruloplasmin [14], diene conjugates (DC - diene conjugates) [15], products of free radical modification of proteins [16], activity of leukocyte elastase [17] and myeloperoxidase [18].

Both the left and right knee were harvested, rinsed with phosphate buffer saline (PBS), and fixed in 10% buffered formalin solution. The samples of capsule, meniscus and epiphysis of the tibia were demineralized in a solution of OsteoFast 2 (BioGnost Ltd., Croatia), dehydrated in alcohol and were embedded in paraffi (Leica Surgipath Paraplast Regular, USA). 8μm microsizes were made on Thermo Microm HM 360 microtome (Thermo Scientific, USA) and stained with hematoxylin and eosin, alcian blue with picrofuchsin and observed with an Olympus BX51 microscope. The Carl Zeiss AxioVision SE64 Rel.4.9.1 software was used for morphometry. We were analyzed density of density of subchondral bone tissue and thickness of perifocal epiphyseal cartilage. Calculations were performed from images of histological slices (×100, ×200).

Structural changes of the knee joint were evaluated using light microscopy and scoring systems: 1) joint capsules according to the criteria: cellular infiltration, intimal hyperplasia, subintimal edema, subintimal fibrosis [19]; 2) epiphyseal cartilage by criteria: cell morphology, proteoglycan (toluidine blue) staining, cartilage thickness, surface regularity, extent of integration of matrix [20]; 3) meniscus by criteria: surface, cartilage cells, collagen fibers [21]

All the experimental manipulations were approved by the Ethics Committee of the State Institution "The Institute of Traumatology and Orthopedics under NAMS of Ukraine". The animal experiment complied with the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (#123, Council of Europe, L222, 24/08/1999, p. 31).

All data are provided as the mean ± standard error of the mean (SEM). Statistical analysis was performed using the SPSS (IBM, USA) and Origin vs 8.0 (OriginLab Corporation, USA). All data were assessed for Gaussian distribution using the Shapiro-Wilk normality test. The differences between the groups were evaluated using one-way analysis of variance, and post hoc Tukey test; Kruskal-Wallis test for nonparametric data. Correlation analysis was performed using Spearman's rank correlation test. Statistical significance was set at $P<0.05$

Results and discussion. To assess the level of damage of the capsule and articular cartilage in 75 days after modeling, these structures of the knee joint were examined by histological method. Observe Fig. 1 for the distribution of values of the experimental groups by type of injected cell suspensions. The McIlwraith scale showed high values in samples with PTOA, mainly, damage to the synovial membrane (alteration of the synovial membrane, synovial villi), equally leukocyte infiltration and fibrosis (subintimal). We did not find intimal hyperplasia, on the contrary, it underwent a significant reduction due to the inflammatory process and impaired regional microcirculation (hemorrhagic penetration into the areas of edema, subintimal edema). The total histological score was statistically lower in the PRP group ($P<0.05$) and BMAC group ($P<0.05$). No difference was found in PRP group vs BMAC group; no difference was found in BMAC group vs PTOA group.

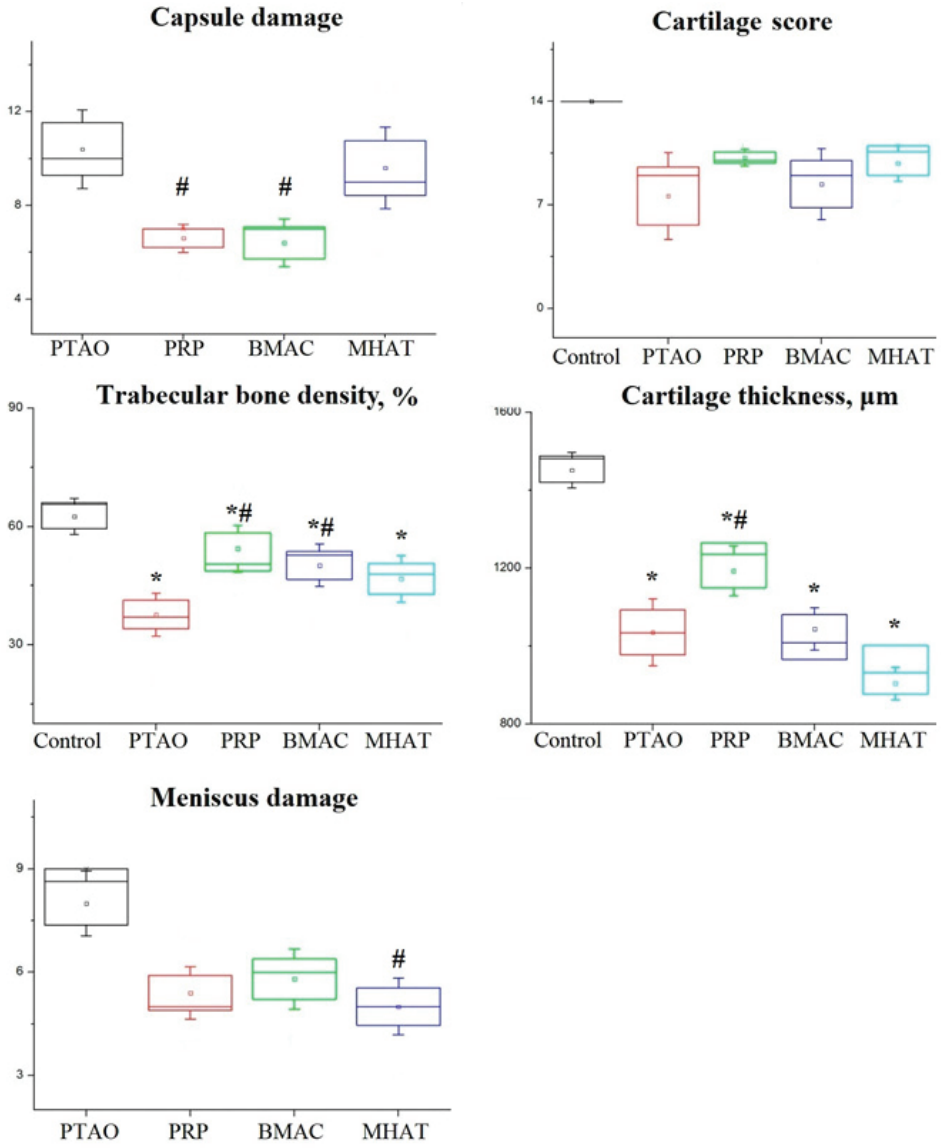

Fig. 1. The results of the assessment of knee joint injury based on a morphometric data and scoring systems. P<0.05 compared to the control group; # P< 0.05 compared to the PTOA group

According to the Fitzgerald scale, the total histological index was equal in all samples with PTOA, the separation of the average thickness of the perifocal cartilage made it possible to detect a statistical differ nce in the PRP group (P<0.05). This shows that the assessment of joint changes by the sum of several indicators (integral indicator) is more important than only individual indicators, such as cartilage thickness or chondrocyte density, such actions may be speculative.

PTOA simulation of osteoarthritis caused traumatic injury and alteration of hyaline cartilage and was reflected in subchondral bone density. The reduction of trabecular bone was at the level of 39.8% (P<0.05). In PRP group (P<0.05) and BMAC group (P<0.05) the indicator was statistically higher vs PTOA group. In addition, there was a direct correlation between subchondral bone damage and cartilage damage (r=1.00; P<0.01) and joint capsules (r=-0.949; P<0.05). Noticeable that the correlation in BMAC group was relative to the values of the joint scale (r=-1.00; P<0.01), in MHAT group relative to the values of the capsule scale (r=-0.949; P<0.05), in PRP group there was no correlation.

Uneven staining of the cartilaginous body of the meniscus was registered in all samples with PTOA, violation of the density of collagen in the capsule of the meniscus, ruptures and deformations, in some samples hemorrhagic impregnation of the connective tissue of the meniscus. The overall rate of histological changes of the meniscus was statistically higher in PTOA group vs PRP group (P<0.05) and MHAT group (P<0.05). In the body of the meniscus there was a greater number of chondrocytes, less deformation and rupture of the cartilage matrix and the preservation of the cell layer of the capsule. In contrast, in the BMAC group the capsule was changed, it was poorly followed, because on the border of the meniscus with the epiphyseal cartilage there was morphogenesis of reticular tissue, its integration with the meniscus capsule. These results indicate that PRP and MHAT reduce meniscus degradation, and the introduction of BMAC had a similar trend, but the scale scores were higher due to reorganisation of the meniscus capsule against the background of morphogenesis and integration of newly-formed reticular tissue around the meniscus (collagen density in the capsule was reorganized).

As expected, damage of the articular cartilage affected blood counts. We predicted that the level of peroxidation products in the blood increases against the inflammation in the joint. Statistically increased activity of leukocyte elastase (114.3%; r=-0.90; P<0.05) and myeloperoxidase (171.4%, P<0.05) and this correlated with the increased levels of TBARS (108.8%; r=-0.90; P<0.05) and DC (69.7%; r=0.90; P<0.05). In addition, the increase of products in plasma of oxidative modification of proteins and ceruloplasmin correlated (44.3%; r=1.00; P<0.01).

Data which refers to the changes in ceruloplasmin levels appeared to be interesting. It turned out that the decrease in ceruloplasmin levels correlates with a higher density of subchondral bone in the PRP group and BMAC group, ie this indicator can predict the direction of the disease, progressive osteoarthritis or the dynamics towards the recovery process.

In the PRP group a statistical decrease in the activity of leukocyte enzymes and products of lipid and protein peroxidation in serum was found (between the latter direct correlation, r=1.00; P<0,01). A negative correlation was discovered between the level of subchondral bone tissue (11.4; P<0.05) and ceruloplasmin (r=1.00, P<0.01), although the level of the latter only had a decreasing trend. The results of PRP can be considered as a means of delaying osteoarthritis, although ceruloplasmin remained at an elevated level.

In BMAC group, a statistically higher density of subchondral bone was found compared to PTOA group, and these values correlated with a decrease in serum TBARS (18.3%; r=-1.00; P<0.01) and DC (25.1%; r=-1.00; P<0.01). Level of serum ceruloplasmin was significantly reduced by 16.5% (P<0.05). Apparently, the level of articular cartilage damage was at the level of the PTOA group, which also correlated with increased leukocyte elastase activity. In contrast, statistically reduced myeloperoxidase activity correlated with a decrease in serum protein oxidation products (r=-1.00, P<0.01). and a decrease in the level of ceruloplasmin (r=1.00, P<0,01), but no dependence was found on the level of damage of the capsule, cartilage and bone tissue (r=-0.50; P≥0.05) of the knee joint. These data indicate that the use of BMAC significantly inhibited the progression of dystrophic changes in the epiphyseal bone, between the knee injury and biochemical parameters of the blood is a direct relationship that can be assessed and predicted.

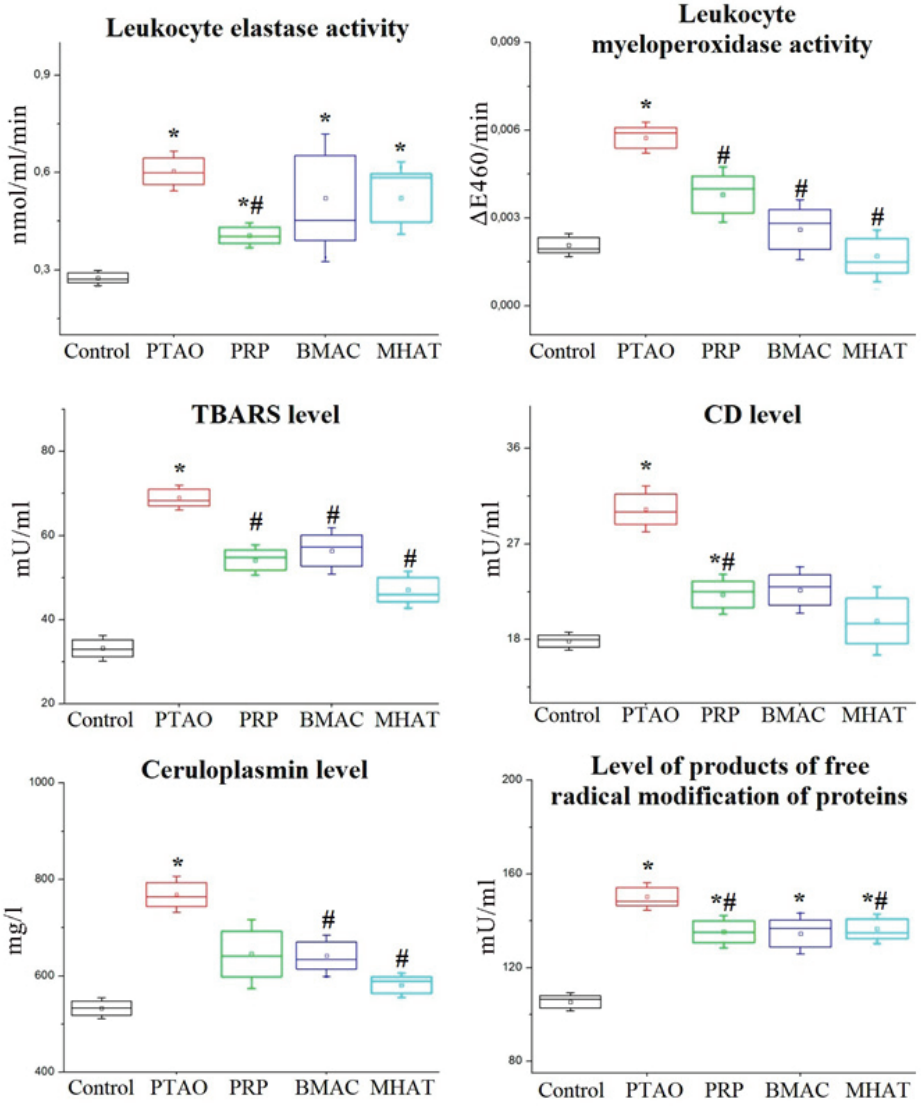

Fig. 2. Activity of the leukocyte enzymes, ceruloplasmin and products of lipid and protein peroxidation. P<0.05 compared to the control group; # P<0.05 compared to the PTOA group

No changes in subchondral bone density relative to the PTOA group were detected in the MHAT group. According to the McIlwraith and Fitzgerald scale, there was also no difference, changes in the capsule correlated with bone damage (25.3%; r=0.949; P<0.05), high levels of leukocyte elastase (85.7%; r=-1.00; P<0.01,) and DC (10.6%; r=0.949; P<0.01). No correlation of myeloperoxidase activity with any of the evaluated indicators was detected. This means that the leukocyte response may be related to other factors, including the response to the MHAT injection.

No correlation was found between all indicators using the Spearman's rank correlation test, but a statistically significant improvement was found for most indicators by the Kruskal-Wallis test or ANOVA. The obtained results on various indicators are somehow "disordered", but if we do not take into account the factor of introduction of cell suspensions, then almost all indicators correlate with each other. This is both evidence of a direct relationship between morphological parameters of joint changes with biochemical parameters of inflammation in the serum in the pathogenesis of osteoarthritis and the manifestation of the influence of cell suspensions on its development

In conclusion, the most significant results in terms of action of cell suspensions can be considered those obtained in the BMAC group. Discussions about the specific action of PRP, BMAC, or MHAT, such as the release of growth factors, are speculative, as there is no evidence as to which cells release specific growth factors. In our work, this was not the aim of the study at all, and the most important participation of the introduced cells affected the activation of connective tissue regeneration of the meniscus of the joint and integration of reticular tissue and adipocytes with the meniscus capsule and synovial membrane. These effects are evidence of the viability of the cells introduced into the damaged joint by activating the regenerative processes in the capsule and meniscus under the action of BMAC and MHAT, while significant morphological evidence of articular cartilage regeneration has not been established. This confirms once again the poor regenerative potential of articular cartilage and therefore treatment should be aimed at preventing the progression of cartilage alteration and bone damage. In this direction, BMAC has the best potential vs MHAT and PRP.

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SUMMARY

CORRELATION OF BLOOD BIOCHEMICAL INDICATORS WITH THE LEVEL OF KNEE JOINT DAMAGE IN THE MODEL OF THE POSTTRAUMATIC OSTEOARTHRITIS

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The aim of the study was to assess the dependence of blood biochemical parameters with the degree of osteoarthritis of the knee joint and therapy. In experiments, osteoarthritis was simulated in rabbits (n=25) and after 75 days changes in the level of peroxidation products, activity of leukocyte enzymes were studied and the results were compared with the degree of knee joint injury, as well as taking into account the application of a concentrate of bone marrow aspirate, mechanically homogenized adipose tissue and platelet rich plasma. Analysis of the results confirmed the assumption of a direct relationship between the level of peroxidation products (diene conjugates, TBA-reactive products, products of oxidative modification of proteins), ceruloplasmin, and proinflammatory activity of leukocytes (by the activity of elastase and myeloperoxidase) with the level of morphological changes in the articular cartilage, capsule and meniscus of the knee joint. Based on histological analysis, it was concluded that the application of a concentrate of bone marrow aspirate and homogenized adipose tissue activated the processes of reorganization and regeneration of the synovial membrane and menisci of the joint, which correlated with the indicators of myeloperoxidase activity, the level of TBA-reactive products and ceruloplasmin. The action of platelet rich plasma was characterized by a correlation between leukocyte enzymes and lipid and protein *oxidation products* in blood serum. The results of the study suggest that the bone marrow aspirate concentrate has a greater therapeutic potential compaired to the platelet rich plasma and cell suspension obtained from adipose tissue.

Keywords: osteoarthritis, biochemical parameters, morphometry, experimental therapy.

РЕЗЮМЕ

ЗАВИСИМОСТЬ БИОХИМИЧЕСКИХ ПОКАЗАТЕЛЕЙ КРОВИ ОТ УРОВНЯ ПОВРЕЖДЕНИЯ КОЛЕННОГО СУСТАВА ПРИ ПОСТТРАВМАТИЧЕСКОМ ОСТЕОАРТРИТЕ

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Цель исследования – оценка зависимости биохимических показателей крови со степенью поражения коленного сустава при остеоартрозе. На кроликах породы Шиншилла весом 3-4 кг (n=25) моделировали остеоартроз, затем спустя 75 дней изучали показатели уровня продуктов пероксидации, активности лейкоцитарных ферментов, результаты сопоставляли со степенью поражения коленного сустава, а также с учетом введения концентрата аспирата костного мозга, механически гомогенированной жировой ткани и тромбоцитарной плазмы.

Анализ полученных результатов подтвердил предположение о прямой зависимости показателей уровня продуктов пероксидации (диеновые коньюгаты, ТБК-реагирующие продукты, продукты окислительной модификации белков), церулоплазмина и провоспалительной активности лейкоцитов (активность эластазы и миелопероксидазы) с уровнем морфологических изменений суставного хряща, капсулы и мениска коленного сустава. На основе гистологического анализа авторами сделан вывод, что введение концентрата аспирата костного мозга и гомогенизированной жировой ткани активирует процессы реорганизации и регенерации синовиальной оболочки и менисков сустава, что коррелирует с показателями активности миелопероксидазы, уровнем ТБК-реагирующих продуктов и церулоплазмина. Действие тромбоцитарной плазмы характеризовалось корреляционной связью лейкоцитарных ферментов и продуктов пероксидации липидов и белков в сыворотке крови. Результаты исследования позволяют предположить, что концентрат аспирата костного мозга имеет более высокий терапевтический потенциал в сравнении с тромбоцитарной плазмой и клеточной суспензией, полученной из жировой ткани.

რეზიუმე

სისხლის ბიოქიმიური მაჩვენებლების დამოკიდებულება მუხლის სახსრის დაზიანების დონეზე ოსტეოართროზის დროს

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კვლევის მიზანს წარმოადგენდა სისხლის ბიოქიმიური მაჩვენებლების დამოკიდებულების შეფასება მუხლის სახსრის დაზიანების დონეზე ოსტეოართროზის დროს.

შინშილას ჯიშის ბოცვერებზე (წონით 3-4 კგ) მოდელირდებოდა ოსტეოართროზი; შემდგომ, 75 დღის შემდეგ შეისწავლებოდა პეროქსიდაციის პროდუქტების მაჩვენებლების დონე და ლეიკოციტური ფერმენტების აქტივობა; მიღებული შედეგები ანალიზდებოდა მუხლის სახსრის დაზიანების ხარისხთან, ძვლის ტვინის ასპირატის კონცენტრატის, მექანიკურად ჰომოგენიზებული ცხიმოვანი ქსოვილის და თრომბოციტული პლაზმის შეყვანის გათვალისწინებით.

მიღებული შედეგების ანალიზით დადასტურდა მოსაზრება პეროქსიდაციის პროდუქტების (დიენური კონიუგატები, თიობარბიტურმჟავაზე მორეაგირე და

ცილების მოდიფიკაციის ჟანგვითი პროდუქტები), ცერულოპლაზმინის და ლეიკოციტების პროანთებითი აქტივობის (ელასტაზას და მიელოპეროქსიდაზას აქტივობა) პირადაპირი დამოკიდებულება სახსრის ხრტილის, მუხლის სახსრის კაფსულის და მენისკის მორფოლოგიური ცვლილებების დონესთან. ჰისტოლოგიური ანალიზის საფუძველზე ავტორები დაასკვნიან, რომ ძვლის ტვინის ასპირატის კონცენტრატის და ჰომოგენიზებული ცხიმოვანი ქსოვილის შეყვანა ააქტივებს სახსრის სინოვიური გარსის და მენისკის რეორგანიზაციისა და რეგენერაციის პროცესებს, რაც კორელირებს მიელოპეროქსიდაზას, თიობარბიტურმჟავაზე მორეაგირე პროდუქტების და ცერულოპლაზმინის აქტივობის მაჩვენებლებთან. თრომბოციტული პლაზმის მოქმედება ხასიათდებოდა კორელაციური კავშირით ლეიკოციტურ ფერმენტებთან და ცხიმებისა და ცილების პეროქსიდაციის პროდუქტებთან სისხლის შრატში. კვლევის შედეგები იძლევა ვარაუდის საფუძველს, რომ ძვლის ტვინის ასპირატის კონცენტრატს აქვს მაღალი თერაპიული პოტენციალი, თრომბოციტულ პლაზმასა და ცხიმოვანი ქსოვილიდან მიღებულ უჯრედულ სუსპენზიასთან შედარებით.

POSSIBLE EFFECTS OF ELECTRIC-MAGNETIC STIMULATION ON HYPOTHALMIC-HYPOPHISIAL-ADRENAL AXIS: BEHAVIOURAL STUDY

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Depression disrupts the physiological and emotional function of the body and can lead to health problems. Potential reactions to the development of depression can be physiological such as cognition, emotion, and behavior. One of the most important physiological responses to depression is the enhanced release of glucocorticoids. Depressed patients consistently exhibit hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis [7,10]. HPA axis activity is regulated by the secretion of the corticotropic hormone-releasing factor (CRF), vasopressin (AVP) and oxytocin (OXY) from the hypothalamus, which finally stimulates the secretion of the glucocorticoids from the adrenal cortex. Glucocorticoids interact with their receptors (GRs) in multiple target tissues including the HPA axis by feedback inhibition [3,6,8,9].

Glucocorticoid receptor modulators and selective glucocorticoid receptor agonists, combined as glucocorticoid receptor agonists. They belong to the class of experimental medications designed as anti-inflammator , immunosuppressive, or anti-tumor medications [1,2].

Selective glucocorticoid receptor agonists are steroidal structures, while selective glucocorticoid receptor modulators are usually nonsteroidal. Both modulators and agonists act by activating glucocorticoid receptors. Dexamethasone is an agonist of glucocorticoid receptors.

Working hypothesis. The activity of the HPA axis increases by the action of large doses of dexamethasone, a glucocorticoid receptor agonist. Thus, we assumed that exposure to GR agonists would reveal depressive behavior. It has been suggested that EMS will reduce the activity of the HPA axis, GR expression, and thus improve the symptoms of a depressed state.

Material and methods. The experiments were conducted on mongrel, albino male rats, weighing 150- 200 g (n=14). Proceeding from the goals set, the experimental group (dexamethasone-treated) and the control group of rats were involved in the experiments. Each group was divided into subgroups. Some rats from the subgroup were given EMS.

Reagents – Dexamethasone - 1mg/ per animal for 10 days were given to the experimental groups The Control group of rats received the same amount of saline.

Electro-Magnetic stimulation —For EMS (carried for 10 consecutive days) the device with coil designed at Tbilisi Technical University, Georgia was used. The parameters of EMS (stimulus frequency, number, and duration of stimuli,) which partially or fully inhibited behavior manifestation of depression, were established during pilot experiments. For repetitive EMS the following parameters: 10000 -15000 Hz frequency, 1,5 m/Tesla, for 15 min, during 10 consecutive days were used.

Forced Swimming Test (FST) - is quite sensitive to antidepressant treatment. In this task, the rats were individually placed in a vertical cylinder containing water (25 0C) for a set length of time (15 min). 24 hours later, the rats were placed in the same cylinder and the time spent immobile, active swimming, struggling/climbing, and spent under the water were measured during a 5 min.

The Open Field Test- Against the background of repeated EMS, the behavioral parameters of emotionally motivated reactions were studied in the open field test. The open field appears to be a chamber with 80 cm diameter, surrounded by 30 cm height walls. The floor is divided into 32 squares and lighted with a 200 W lamp. The observation of the rats took place for 5 minutes at the same time of the day. The video registration of the following parameters: entering the center, number of crossed squares, head raise, vertical stands, the frequency and duration of grooming, number of fecal boluses, and urination were performed. After each experiment, the experimental chamber was cleaned with a 30% ethanol solution.

Active Wheel Test- allows rats to run freely on the open surface of a wheel which rotated freely around its axis. The active wheel is equipped with a magnetic counter, so that frequency and rate of running can be monitored and analyzed for variable periods. All rats were placed individually in a wheel for 24 hours. So, an accurate recording was made for each animal. In the active wheel test, water and food were given to rats without any restriction.

The obtained results were processed using an adequate statistical program. Data reliability was assessed using parametric and non-parametric techniques, with the use of one- and two-way layout of factorial analysis.

Results and discussion. *Impact of EMS on the level of depression and anxiety reaction of rats in dexamethasone-treated rats*

In FST on the background of dexamethasone injection, the time of immobilization ($p<0.01$) was increased, the active swimming time ($p<0.05$), the time of the struggling/climbing ($p<0.05$) and the time spent under the water ($p<0.05$) were decreased compared to non-treated rats. This fact indicates the development of depressive-like behavior. The EMS reduced immobility time in the FST ($p<0.01$) in the dexamethasone-treated rat. The EMS increased struggling behavior ($p<0.05$), active swimming in the FST ($p<0.05$), and the time spent under the water ($p<0.05$) (Fig. 1).

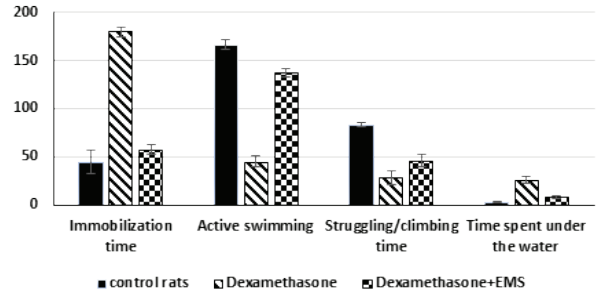


Fig.1. The effects of EMS on dexamethasone-treated rat's behavior in the FST. Black columns - a control group of inbred rats. Shaded columns (1) – an experimental group of white inbred rats after dexamethasone injection, (2) white, inbred dexamethasone-treated rats after EMS

Against the background of EMS, the latent period of immobilization has also increased from 25 to 95 sec (Fig.2).

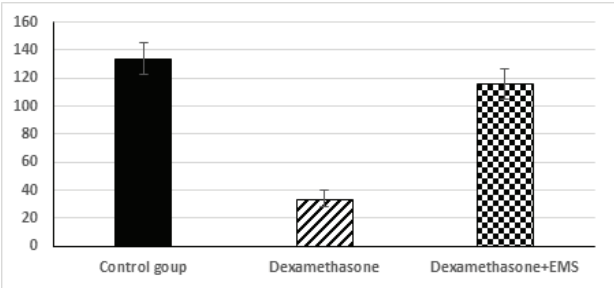


Fig.2. Latent period of immobilization in FST. Black columns - a control group of inbred rats. Shaded columns (1) – an experimental group of white inbred rats after dexamethasone injection, (2) white, inbred dexamethasone-treated rats after EMS

These findings suggest that acoustic range EMS decreases fear and anxiety degree and consequently, increases the escape activity in FST. Thus, In the control, non-treated rats, active strategies (climbing and swimming) were predominant. dexamethasone-treated rats, in the inescapable aversive situation, selected passive strategies of coping. The obtained behavioral parameters indicate that the degree of depression increased with the introduction of a glucocorticoid agonist - dexamethasone.

The EMS could increase the number of active strategies of dexamethasone-treated rats in the FST. Reduced immobilization time, increased time of active swimming, and time spent trying to climb the wall, reduced time underwater take us opportunity to decided that EMS had the potential to predict its efficac like the antidepressant. Therefore, EMS has a positive effect on the body and reduces the degree of depression.

Impact of EMS on the motivational-behavioral activity in the open field in dexamethasone-treated rats.

To determine the motivational-behavioral activity of rats after dexamethasone treatment, the open field Test was choosing. The open field allows us to simultaneously measure the locomotor and research activity of rats, as well as to judge the degree of the alarm of rats. For example, an increase in the number of crossed squares, vertical stands, the number of entrances to the center, and the extension of time of grooming indicate increased locomotor research activity and a reduction in the alarm response;

Excessive stress and glucocorticoids cause movement disorders and pathologies of the motor system in general. It has been established, that Glucocorticoid receptors (GRs) affect depression-like behavior caused by stress. However, part of the science points to the role of mineralocorticoids in modulating stress-induced behavior. Dexamethasone mainly effects on glucocorticoid receptors [8].

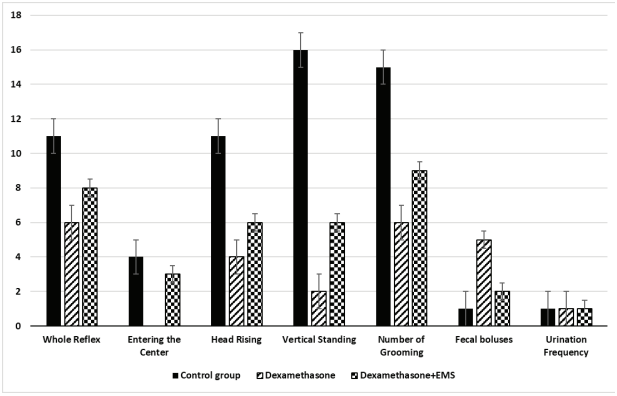
The Injection of Dexamethasone caused changes in the motivational-emotional behavior of rats. All parameters of research-motor activity were reduced compared to normal (untreated) rats. In particular, locomotor research activity decreased from 145 to 25 ($P\leq0.01$), entry to the center decreased from 4 to 0, the number of head raise increased from 11 to 4 ($P\leq0.05$), and vertical standing decreased from 16- to 2 ($P\leq0.01$).

The number (from 15 to 6 sec) and the duration (from 46 to 25 sec) of grooming were also reduced ($P\leq0.05$). The number of fecal boluses increased ($P\leq0.05$). The frequency of urination in experimental rats did not change compared with the control group.

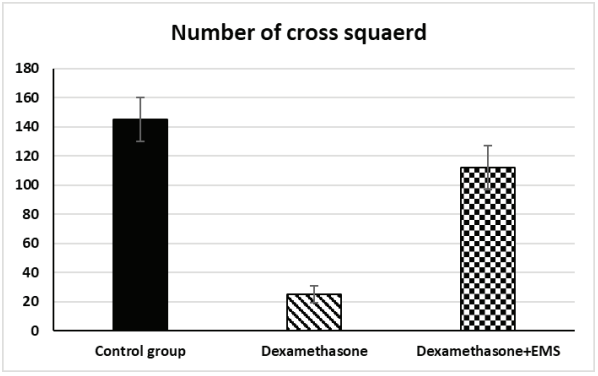
The EMS, after dexamethasone injection, enhanced research-motivated behavior of rats: crossed square (from 25 to 112, $P\leq0.01$), entry to the center (from 0 to 3, $P\leq0.05$), the number of vertical standing (from 4 to 6, $P\leq0.05$), and as well as grooming episodes (from 6 to 9, $P\leq0.05$), therefore, increased the total duration of the grooming (Fig.3). Grooming is a substitute reaction that arises during emotional tension and is a means of emotional relief. The number of fecal boluses decreased. The frequency of urination did not change. We can assume that EMS strengthens the self-regulatory mechanisms, which increases the resistance of the organism to stress factors, in this case, under the conditions of artificial administration of dexamethasone

Impact of EMS on the motivational-behavioral activity in the Active Wheel Test in dexamethasone-treated rats.

The behavior of rats on the active wheel includes defensive behavior, aggressive behavior, as well as the behavior associated with depression and anxiety. Areas of the brain that are involved in stressful reactions also are involved in being active on the wheel. In general, the behavior on an active wheel requires the integration of various vital functions that may alter the body's behavior and physiology. After 10 days of administration of dexamethasone, the locomotor activity of rats was significantly reduced during the 24-hour active wheel test. On the background of EMS, the motor activity dramatically increased in dexamethasone-treated rats (Fig. 4).



a



b

Fig.3 (a, b) The effects of EMS on the locomotor and exploratory activity of dexamethasone-treated rats in the open field test. Black columns - a control group of inbred rats; shaded columns (1) – an experimental group of white inbred rats after dexamethasone, (2) white, inbred dexamethasone-treated rats after EMS

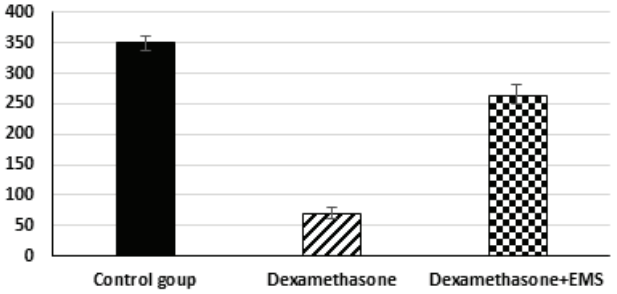


Fig. 4. The effects of EMS on the locomotor activity of dexamethasone-treated rats in the active wheel Test. Black columns - a control group of inbred rats. Shaded columns (1) – an experimental group of white inbred rats after dexamethasone), (2) white, inbred dexamethasone-treated rats after EMS

Depression change activity of corticosteroid receptors that gives causes an excessive release of neurohormones (glucocorticoids) and some of the symptoms characteristic of depression can be detected. in the same way, multiply injection of high doses of dexamethasone also will have a similar effect. In the brain, receptors for corticosteroids, glucocorticoids (GR), and mineralocorticoids (MR) can act through a classic, genomic mechanism to elicit changes in behavior and physiology, and these receptors can further function at the membrane to activate cytoplasmic signaling pathways [4, 6].

It is possible to assume that EMS exerts antidepressant effects against the background of dexamethasone injection and inhibits the activity of the hypothalamic-pituitary-adrenal system. Therefore, the corticosteroid receptor function is improved. It is known that activated by ligands, corticosteroid receptors act as transcription factors in correspondence with numerous other transcription factors already known to be activated by antidepressants [3]. Therefore, the drugs or artificially created electric-magnetic field that interfere more directly with stress hormone regulation, such as corticosteroid receptor antagonists and corticotropin-releasing hormone receptor antagonists reduced depression-like behavior of rats.

Conclusion. Against the background of high doses of dexamethasone, EMS causes the body to become more active, change the depressive-like behavior, reduces the alarm response, and increases research activity.

We suppose that EMS suppresses the GRs expression (negative feedback) which reduces the activity of the HPA axis and recover behavioral disorders induced by depression.

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creases depression-like behavior and modulates neuroendocrine and central hypothalamic-pituitary-adrenocortical axis responsiveness to stress. // Psychoneuroendocrinology 2010, 35, 1100–1112.

SUMMARY

POSSIBLE EFFECTS OF ELECTRIC-MAGNETIC STIMULATION ON HYPOTHALMIC-HYPOPHISIAL-ADRENAL AXIS: BEHAVIOURAL STUDY

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The goal of this investigation was to study the effect of the electric-magnetic stimulation (EMS) on the activity of the HPA axis, which can change behavior activity.

The experiments were conducted on mongrel, albino male rats, weighing 150- 200 g (n=14). Proceeding from the goals set, the experimental group (dexamethasone-treated-1mg/ per animal for 10 days) and the control group of rats were involved in the experiments. Each group was divided into subgroups. Some rats from the subgroup were given EMS. The Control group of rats received the same amount of saline. Electro-Magnetic stimulation parameters: 10000 -15000 Hz frequency, 1,5 m/Tesla, for 15 min, during 10 consecutive days. The Forced Swimming, the Open Field, and the Active Wheel Tests were choosing for monitoring of behavior indicators. The obtained results were processed using an adequate statistical program.

1. In FST on the background of dexamethasone injection, the time of immobilization ($p<0.01$) was increased, the active swimming time ($p<0.05$), the time of the struggling ($p<0.05$) and the time spent under the water ($p<0.05$) were decreased. This fact indicates the development of depressive-like behavior. The EMS reduced immobility time in the FST ($p<0.01$) and increased struggling behavior ($p<0.05$), swimming in the FST ($p<0.05$), and the time spent under the water in the dexamethasone-treated rat. The Injection of Dexamethasone caused changes in motivational-emotional behavior in Open Field Test: all parameters of research-motor activity were reduced compared to normal (untreated) rats. The EMS after dexamethasone injection enhanced behavior activity of rats: research-motivated activity. We can assume that EMS strengthens self-regulatory mechanisms, which increases the resistance of the organism to stress factors, in this case, under the conditions of artificial administration of dexamethasone. 3. After 10 days of administration of dexamethasone, the locomotor activity of rats was significantly reduced during the 24-hour active wheel test. On the background EMS the motor activity dramatically increased in dexamethasone-treated rats It is possible to assume that EMS exerts antidepressant effects against the background of dexamethasone injection and inhibits the activity of the hypothalamic-pituitary-adrenal system.

Against the background of high doses of dexamethasone, EMS causes the body to become more active, change the depressive-like behavior, reduces the alarm response, and increases research activity. We suppose that EMS suppresses the GRs expression (negative feedback) which reduces the activity of the HPA axis, and recover behavioral disorders induced by depression.

Keywords: electric-magnetic stimulation, Dexamethasone, depression.

РЕЗЮМЕ

ВОЗМОЖНОЕ ДЕЙСТВИЕ ЭЛЕКТРОМАГНИТНОЙ СТИМУЛЯЦИИ НА ГИПОТАЛАМО-ГИПОФИЗАРНО-НАДПОЧЕЧНИКОВУЮ ОСЬ: ПОВЕДЕНЧЕСКОЕ ИССЛЕДОВАНИЕ

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Депрессия нарушает физиологическую и эмоциональную функцию организма и может привести к проблемам со здоровьем. Пациенты с депрессией проявляют гиперактивность гипоталамо-гипофирно-надпочечниковой (HPA) оси. Активность HPA оси регулируется секрецией кортикотропин-рилизинг-фактора (CRF), который в конечном итоге стимулирует секрецию глюкокортикоидов из коры надпочечников. Электромагнитная стимуляция (EMS) является неинвазивным методом лечения, его используют в качестве дополнения к лекарственным препаратам для лечения различных нейродегенеративных заболеваний.

Целью исследования явилось изучение влияния электромагнитной стимуляцим на активность гипоталамо-гипофирно-надпочечниковой оси, которая может изменить поведение.

Эксперименты проводились на беспородных крысах-самцах весом 150-200 г (n=14). Опыты проводились на экспериментальной группе животных, которым вводили дексаметазон в дозе 1 мг в течение 10 дней и контрольной группе крыс. Каждая группа разделена на подгруппы. Некоторые крысы из подгруппы подвергались EMS: частота 10000-15000 Гц, 1,5 м/Тесла, в течение 15 минут, 10 дней подряд. Тесты принудительного плавания (FST), открытого поля и активных колес проводились для мониторинга параметров поведения. Полученные результаты обработаны с использованием адекватной статистической программы.

В FST, на фоне инъекции дексаметазона, увеличено время иммобилизации ($p<0,01$). Время активного плавания ($p<0,05$), время потраченное на попытки подняться на стену ($p<0,05$) и время, проведенное под водой ($p<0,05$) уменьшились, что указывает на развитие депрессивно-подобного поведения. EMS уменьшала время неподвижного состояния ($p<0,01$) и увеличивала время активного плавания ($p<0,05$) и время, проведенное под водой. Инъекция дексаметазона вызывала изменения в мотивационно-эмоциональном поведении крыс в тесте открытого поля: все параметры исследовательско-двигательной активности были снижены в сравнении с контрольными крысами. EMS после введения дексаметазона усиливала поведенческую активность крыс. Следует предположить, что EMS усиливает саморегулирующие механизмы, повышает устойчивость организма к стрессовым факторам, в данном случае, в условиях искусственного введения дексаметазона.

После 10-дневного введения дексаметазона двигательная активность крыс значительно снижалась в течение 24-часового наблюдения в тесте активного колеса. На фоне EMSдвигательная активность резко возросла. Следует предположить, что EMS оказывает антидепрессивное действие

на фоне инъекций дексаметазона и угнетает деятельность гипоталамо-гипофизарно-надпочечниковой системы.

На фоне высоких доз дексаметазона, EMS усиливает саморегулирующие механизмы, повышает устойчивость и активность организма, снижает реакцию на тревогу и увеличивает исследовательскую активность. Авторы предполагают, что EMS подавляет экспрессию глюкокортикоидных рецепторов, которая снижает активность HPA оси и восстанавливает поведенческие расстройства, вызванные депрессией.

რეზიუმე

ჰიპოთალამურ-ჰიპოფიზურ-ადრენალურ ღერძზე ელექტრომაგნიტური სტიმულაციის შესაძლო ზემოქმედება: ქცევითი გამოკვლევა

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დეპრესია არღვევს სხეულის ფიზიოლოგიურ და ემოციურ ფუნქციონირებას და შეიძლება გამოიწვიოს ჯანმრთელობის პრობლემები. დეპრესიის მქონე პაციენტებში ხშირია ჰიპოთალამურ-ჰიპოფიზურ-ადრენალური (HPA) ღერძის ჰიპერაქტიურობა. HPA ღერძი რეგულირდება კორტიკოტროპინ გამათავისუფლებელი ფაქტორის სეკრეციით, რაც საბოლოოდ ასტიმულირებს გლუკოკორტიკოიდების სეკრეციას თირკმელზედა ჯირკვლის ქერქიდან. ელექტრომაგნიტური სტიმუ-ლაცია (EMS) არის არაინვაზიური მკურნალობის მეთოდი, იგი გამოიყენება როგორც მედიკამენტების დანამატი სხვადასხვა ნეიროდეგენერაციული და-ავადებების სამკურნალოდ.

კვლევის მიზანს წარმოადგენდა ჰიპოთალამურ-ჰიპოფიზურ-ადრენალური ღერძის აქტივობაზე ელექტრომაგნიტური სტიმულაციის ეფექტის შესწავლა, რამაც შეიძლება შეცვალოს ინდივიდის ქცევა.

ექსპერიმენტები ჩატარდა უჯიშო,მამრი ვირთაგვების 2 ჯგუფზე, წონით 150-200 გ (n=14): ექსპერიმენტულ ჯგუფს უკეთდებოდა დექსამეტაზონი 1 მგ ცხოველზე 10 დღის განმავლობაში, საკონტროლო ჯგუფს კი - იგივე მოცულობის ფიზიოლოგიური ხსნარი. თითოეული ჯგუფი დაყოფილი იყო ქვეჯგუფებად. ქვეჯგუფებიდან ვირთაგვების ნაწილს უტარდებოდა EMS: სიხშირე 10000-15000 ჰც, 1.5 მ/ტესლა, 15 წუთის განმავლობაში, ზედიზედ 10 დღე. იძულებითი ცურვის (FST), ღია ველის და აქტიური ბორბლის ტესტები შერჩეული იყო ქცევის პარამეტრების მონიტორინგისთვის. შედეგები დამუშავდა ადექვატური სტატისტიკური პროგრამის გამოყენებით.

FST-ში დექსამეტაზონის ინექციის ფონზე გაიზარდა იმობილიზაციის დრო ($p<0.01$). შემცირდა აქტიური ცურვის დრო ($p<0.05$), კედელზე ასვლის მცდელობაზე დახარჯული დრო ($p<0.05$), ასევე წყლის ქვეშ გატარებული დრო ($p<0.05$). ეს ფაქტი მიუთითებს დეპრესიული ქცევის განვითარებაზე. EMS-ით შემცირდა წყალში იმობილიზაციის დრო ($p<0.01$), გაიზარდა აქტიური ცურვის დრო ($p<0.05$) და წყლის ქვეშ გატარებული დრო. დექსამეტაზონის ინექციამ შეამცირა ვირთაგვების ემოციურ-მოტივაციური ქცევა ღია ველის ტესტში საკონტროლო ვირთაგვებთან შედარებით. EMS-ით გაძლიერდა ვირთაგვების ქცევითი გამოვლინების ყველა პარამეტრი. შეიძლება ვივარაუდოთ, რომ EMS აძლიერებს თვითრეგულირების მექანიზმებს, ზრდის სხეულის წინააღმდეგობას სტრესის ფაქტორების მიმართ, ჩვენს შემთხვევაში, დექსამეტაზონის დიდი დოზით შეყვანის პირობებში.

დექსამეტაზონის შეყვანიდან 10 დღის შემდეგ ვირთაგვების ლოკომოტორული აქტივობა მნიშვნელოვნად შემცირდა 24-საათიანი დაკვირვების დროს აქტიური ბორბლის ტესტში. EMS-ის ფონზე მკვეთრად გაიზარდა ვირთაგვების აქტივობა. შეიძლება ვივარაუდოთ, რომ დექსამეტაზონის ინიექციების ფონზე EMS-ს აქვს ანტიდეპრესული ეფექტი და აფერხებს ჰიპოთალამურ-ჰიპოფიზურ-ადრენალური ღერძის აქტივობას.

დექსამეტაზონის მაღალი დოზების ფონზე EMS აძლიერებს თვითრეგულირების მექანიზმებს, ზრდის ორგანიზმის მდგრადობას და აქტივობას, ამცირებს შფოთვით რეაქციებს და აძლიერებს ემოციურ-მოტივაციურ კვლევით აქტივობას. ავტორებს მიაჩნიათ, რომ EMS აფერხებს გლუკოკორტიკოიდული რეცეპტორების ექსპრესიას, რაც ამცირებს HPA ღერძის აქტივობას და აღადგენს დეპრესიით გამოწვეულ ქცევით დარღვევებს.

БИОЛОГИЧЕСКАЯ ГЕРМЕТИЧНОСТЬ, МЕХАНИЧЕСКАЯ ПРОЧНОСТЬ И МОРФОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ ОДНОРЯДНОГО И ДВУХРЯДНОГО ТОЛСТОКИШЕЧНОГО ШВА

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Среди заболеваний ободочной кишки, которые подлежат хирургической коррекции, приоритетными по частоте и тяжести считаются злокачественные новообразования ободочной кишки, неопухолевые процессы, такие как дивертикулез, долихосигма, полипоз, воспалительные заболевания толстой кишки, хронический толстокишечный стаз, и, в том числе, стомированные больные. Количество случаев заболеваемости раком толстой кишки в Украине постоянно увеличивается и на сегодняшний день занимают третье место в структуре онкологических заболеваний [4,12]. Ежегодно в мире заболевает 15-18 человек на 100 000 населения [12]. Смертность при этой локализации рака по сей день остается высокой и не проявляет тенденции к снижению. В США колоректальный рак является причиной смерти 3,4% лиц общей популяции и второй по частоте среди причин смерти [12].

Одной из причин смерти является несостоятельность анастомозов в хирургии ободочной кишки, которая составляет 11-12% [5-7,11]. Среди многочисленных факторов, которые вносят свой вклад в несостоятельность анастомозов при хирургии ободочной кишки, следует отнести хирургическую технику [2,10,11]. Все методы формирования толстокишечных анастомозов (ТКА) можно разделить на ручные и аппаратные. При этом дебаты вокруг преимущества однорядного против двухрядного, ручного против аппаратного и преимущества какого-либо другого метода и их модификации продолжаются по сей день, однако так и не получено доказательств преимущества одного метода перед другим [5,6,10]. Идеально, с точки зрения хирургической техники, выполненное хирургическое вмешательство на ободочной кишке не исключает возможность развития несостоятельности анастомоза [11]. Несмотря на большое количество исследований, посвященных определению факторов риска несостоятельности, таких как характер микроциркуляции в зоне анастомоза, уровень загрязнения, техника формирования, внутрикишечное давление, расстояние анастомоза от анального канала, подготовка кишки, способ дренирования брюшной полости, точного ответа на причину несостоятельности не найдено [3,8-11].

В связи с чем попытка улучшить результаты хирургического лечения заболеваний ободочной кишки путем разработки и внедрения новых способов формирования анастомозов является весьма актуальной.

Цель исследования - сравнительная характеристика биологической герметичности, механической прочности и различий морфологических характеристик однорядного и двухрядного толстокишечного швов.

Материал и методы. В операционной ветеринарной клинике «Ветсервис» г. Ужгород проведены исследования на 20 животных. Исследование проведено с соблюдением этических принципов проведения науко-метрических исследований, определенных декларацией Хельсинской Всемирной ассоциации (1964-2008 гг.), и в соответствии этических принципов Европейской конвенции о защите позвоночных животных, используемых для экспериментов или в иных научных целях (Страсбург, 18 марта, 1986 года) и комиссии по этике Закарпатской областной клинической больницы им. Андрея Новака (2008 г.).

Проведено сравнительное морфологическое исследование оригинального и традиционного двухрядного толстокишечного анастомоза, с оценкой их механической прочности и биологической герметичности.

В качестве подопытных животных использованы кролики породы Полтавское серебро (Poltava Silver), вид – Европейский кролик (Oryctolagus cuniculus), обоих полов в возрасте от 8 месяцев до 1,5 года, весом от 1,5 до 2,6 кг [1]. Животные были разделены на 2 группы – опытную (n=10) и контрольную (n=10).

Накануне операции животных не кормили. Для премедикации за 20-30 минут до операции вводили раствор димедрола (1,5 мг/кг) и анальгина (50 мг/кг). Оперативное вмешательство проводили в условиях экспериментальной операционной с соблюдением условий асептики комбинированным наркозом (кетамин 50 мг/кг внутримышечно + масочный эфирный наркоз).

После релапаротомии животных усыпляли методом быстрого введения 7,5% раствора хлорида калия в дозе 1-2 ммоль/кг внутривенно на фоне общего наркоза.

На 1, 3, 5 и 7 сутки выполняли макроскопическую оценку и забор материала для микроскопии линии анастомоза. Макроскопическое описание базировалось на протоколах операций. Полученный материал фиксировался в 10% растворе нейтрального формалина, проводили в спиртах возрастающей крепости и заливали в парафиновые блоки. Депарафинированные срезы толщиной до 4-5 мкм окрашивали гематоксилином и эозином для исследования гистологической картины в свете и фотографировались.

В подопытной группе использовали разработанную методику формирования ТКА, в контрольной – традиционный двухрядный узловой шов.

Оценку механической прочности определяли с помощью оригинальной методики пневмопрессии сегмента толстой кишки с анастомозом. После ревизии пережимали сегмент толстой кишки с анастомозом, отступив 5 см в проксимальном и 5 см в дистальном направлениях. Прокалывали внутримышечной иглой сегмент толстой кишки с присоединенной к ней грушей для нагнетания воздуха и манометром давления. Брюшную полость заполняли физиологическим раствором. Грушей нагнетали воздух в просвет сегмента кишки до появления пузырьков в зоне анастомоза, что свидетельствовало о расхождение краев анастомоза и потере герметичности. На манометре фиксировали уровень давления в миллиметрах ртутного столба, при котором происходило выделение пузырьков воздуха. Данный уровень давления был показателем реальной механической прочности анастомоза (рис. 1).

Степень биологической герметичности определяли через 1, 3, 5 и 7 суток. Линию анастомоза орошали стерильным физиологическим раствором, промывные воды собирали в стерильные пробирки. В течение первых двух часов в условиях бактериологической лаборатории промывные воды сеяли на среды Эндо, Сабуро, кровяной агар, желтково-со-

левой агар, тиогликолевую среду и помещали в термостат. Видовую идентификацию выделенных микроорганизмов проводили через двое суток с помощью тест-систем. Количество колониеобразующих единиц (КОЕ) вычисляли количественным методом.

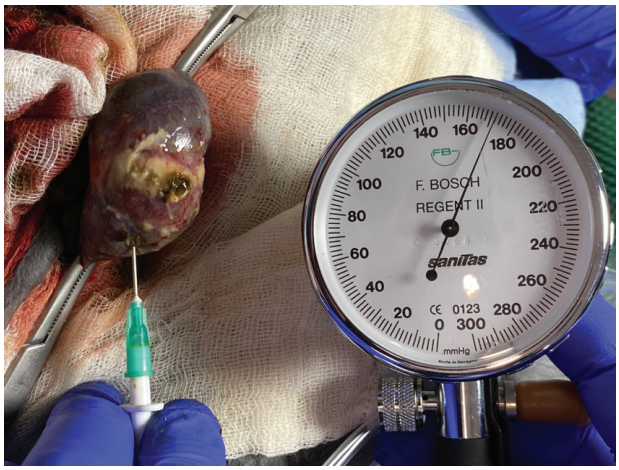

Рис. 1. Интраоперационное фото. Пневмопрессия 172 мм рт.ст. Анастомоз целый

После обработки операционного поля выполняли срединную лапаротомию и выводили петлю ободочной кишки. Пересекали толстую кишку, достигали гемостаза и после подготовки дистальной и проксимальной культи приступали к формированию анастомоза.

Однорядный внутриузловой шов реализуется с использованием атравматического шовного материала (дексон 4/0). Шов выполняется при помощи захвата подслизистого и серозно-мышечного слоев стенки толстой кишки. Вкалывание иглы осуществлялось через подслизистую основу участка кишки, выкалывание – на его серозной оболочке; после чего осуществляется прошивание края анастомозируемого участка от серозной оболочки до подслизистого слоя. Вкалывание проведено через подслизистый слой, расположенный по линии разреза, на границе слизистого и мышечного слоев. Выкол на серозную оболочку находится на расстоянии почти 0,8 см от края рассеченной кишки и, соответственно, первого вкола. Далее, вкалывание со стороны дистального отрезка кишки проводится в 0,8 см от границы пересечения. Выкол располагается на границе слизистой и подслизистой оболочки. Таким образом, при завязывании, узлы располагаются в просвете кишки. Расстояние между отдельными швами составляет около 0,3 см. Швы завязываются после формирования задней губы анастомоза. При формировании передней губы вкол и выкол иглы с прошиванием вышеуказанных слоев осуществляется аналогично. Последний узел, серозно-мышечный, накладывается и завязывается узелком наружу, укрепляя последний внутриузловой шов, наложенный по описанной методике.

В контрольной группе после резекции сегмента кишки ТКА формировали по типу «конец в конец» двухрядными узловыми швами. Применяли медицинский шелк №3. Первый ряд накладывали через все слои стенки кишки, второй ряд – серозно-мышечные швы. Сегмент ободочной кишки со сформированным анастомозом погружали в брюшную полость. Лапаротомную рану послойно зашивали.

Результаты и обсуждение. Динамику *механической прочности* в опытной и контрольной группах исследовали у 18 животных: через сутки - у 4, через трое суток – у 5; через пять суток – у 5; через семь суток – у 4 экспериментальных животных (таблица 1).

Из таблицы 1 явствует, что механическая прочность однорядного ручного анастомоза повышается на каждом этапе исследования, в первые сутки на 66,3%, третьи – 87,6%, пятые – 76,1%, седьмые – 85,4%.

Оценка *биологической герметичности* проводилась у 18 экспериментальных животных: 10 – в опытной группе и 8 – в контрольной группе. Через сутки у – 4; 3 суток – у 5, 5 суток - у 5; 7 суток – у 4 животных. В контрольной группе через сутки с линии анастомозов у 2 животных высеялись колонии E.coli от $3,5x10^5$ до $4,4x10^5$ КОЕ. Через трое суток в 1 случае высеялись колонии E.coli от $3,4x10^4$ до $6,0x10^4$ КОЕ, у 1 животного посевы были стерильными; у 1 экспериментального животного контрольной группы развилась несостоятельность анастомоза. Определение биологической герметичности в данном случае было нецелесообразным. Через 5 суток в 2 наблюдениях посевы были стерильными, в 1 случае отмечена несостоятельность анастомоза. На седьмые сутки у всех животных контрольной группы посевы были стерильными. В опытной группе во все сроки забора материала посевы у всех 10 животных были стерильными.

Макроскопически в контрольной группе через сутки после операции в брюшной полости выявлено небольшое количество (до 15-20 мл) серозного выпота, незначительный отек, легкая гиперемия брюшинного покрова в зоне вмешательства, инъекция сосудов. В области анастомоза выраженная гиперемия, инъекция сосудов, отек серозной оболочки кишки. Швы способны во всех наблюдениях. У 1 животного в области анастомоза определялся налет фибрина, который легко снимался.

На 3 сутки при ревизии в брюшной полости сохранялся серозный выпот. Среднее количество выпота составило 10-15 мл. Сохранялись гиперемия, отечность брюшинного покрова, более выраженная в зоне анастомоза. При этом воспалительные явления усиливались в сравнении с макроскопической картиной первых послеоперационных суток. В области анастомоза отмечались значительная гиперемия, сосудистая реакция, отек и инфильтрация тканей, деформация кишечной трубки, увеличение просвета за счет пареза.

Таблица 1. Сравнительная характеристика механической прочности оригинального и традиционного толстокишечных анастомозов

Период исследования	Средние показатели пневмопрессии (мм рт.ст.)		p-значение
	Опытная группа	Контрольная группа	
Первые сутки	191,5 ± 3,5	115,1 ± 6,5	p=0,004
Третьи сутки	201,3 ± 9,1	107,3 ± 3,7	p<0,001
Пятые сутки	222,5 ± 11,1	126,3 ± 5,5	p=0,002
Седьмые сутки	311,0 ± 18,5	167,7 ± 7,5	p=0,009

У 2 животных по линии анастомоза обнаружен фибриновый налет, который легко удалялся.

У 1 кролика развилась клиника несостоятельности толстокишечного анастомоза с явлениями калового перитонита. После ликвидации несостоятельности и перитонита, данное животное выведено из эксперимента.

На 5-7 сутки в обеих группах в зоне анастомоза определялся спаечный процесс – висцеро-висцеральные и висцеро-париетальные сращения. В контрольной группе спайки носили массивный характер, тогда как в опытной – спаечный процесс был представлен единичными плоскостными спайками. На пятые сутки в контрольной группе при релапаротомии количество выпота в брюшной полости составило не более 5-10 мл. Регрессировали явления воспаления. Брюшина была незначительно гиперемирована, отмечались умеренный отек и единичная инъекция сосудов. В зоне анастомоза сохранялся плотный отек, незначительная гиперемия, сосудистая реакция. Фибриновый налет отделялся трудно и наблюдался у 2 экспериментальных животных. У 1 кролика выявлена несостоятельность анастомоза, осложненная каловым перитонитом. Ликвидация несостоятельности. Это животное также выведено из эксперимента.

На 7 сутки при макроскопической оценке выпот в брюшной полости отсутствовал, гиперемия, отек и инфильтрация брюшины были незначительными, сохранялись только в области анастомоза. Анастомоз покрыт фибрином у всех животных. Несостоятельности анастомоза в этот срок не выявлено.

В опытной группе при ревизии брюшной полости в первые сутки после операции выявлено около 15-20 мл светлого серозного выпота, легкая гиперемия, отек брюшинного покрова в области вмешательства; в небольшом количестве нити фибрина, которые легко удалялись. Наслоения фибрина обнаружены у обоих животных. Стенка кишки незначительно гиперемирована, отечная, умеренная сосудистая реакция.

На 3 сутки в брюшной полости кроликов в опытной группе обнаружено до 10-15 мл серозного выпота. В брюшной полости и в зоне анастомоза равномерно усилились местные воспалительные явления. В области анастомоза более выражены гиперемия, отек, инфильтрация брюшины и стенки кишки. Фибриновый налет отмечен у 2 кроликов.

До 5 суток в опытной группе несостоятельности или прорезывания швов не обнаружено ни в одном наблюдении. В брюшной полости около 5-10 мл серозного выпота. Воспалительные явления регрессировали в значительной степени. Участки гиперемии, инфильтрации и сосудистой инъекции выявлены только в зоне анастомоза. Анастомоз был свободно проходимый, его зона не деформировала кишечную трубку.

На 7 сутки в этой группе выпот в брюшной полости отсутствовал. При ревизии брюшной полости обнаружены незначительная гиперемия и мягкоэластичный отек в зоне, прилегающей к анастомозу, рыхлые спаечные сращения. Несостоятельности швов не отмечено. Незначительная сосудистая реакция непосредственно в зоне анастомоза.

При исследовании морфологической картины анастомоза с использованием оригинальной методики в первые сутки выявлялось нарушение крово- и лимфооттока, что проявлялось отеком подслизистой оболочки. Наблюдались признаки начала гнойного воспаления. В зоне анастомоза накапливались сегментоядерные лейкоциты, определялись участки некроза. Среди них оказалась в небольшом количестве лимфоидно-клеточная инфильтрация. Серозная оболочка покрыта нитями фибрина (рис. 2).

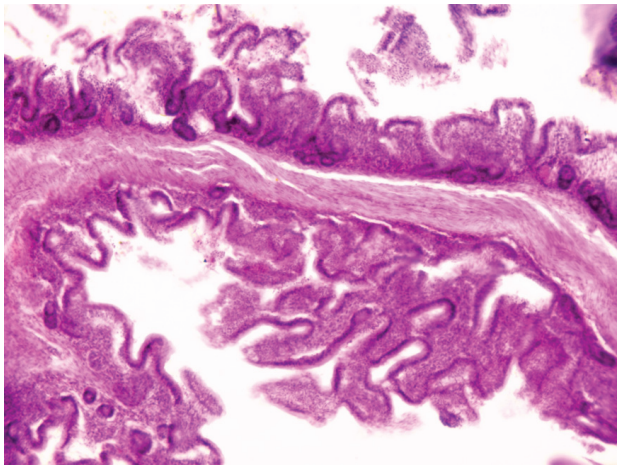

Рис. 2. Морфологическая картина анастомоза опытной группы спустя 24 часа после операции. Окраска гематоксилином и эозином. Увеличение x160. Слизистая оболочка без особенностей, мышечный слой отекший, парезы сосудов со стазом крови в просветах, воспалительная инфильтрация выражена незначительно

При этом количество сегментоядерных лейкоцитов была значительно больше в контрольной группе, что свидетельствует о более сильной воспалительной реакции (рис. 3).

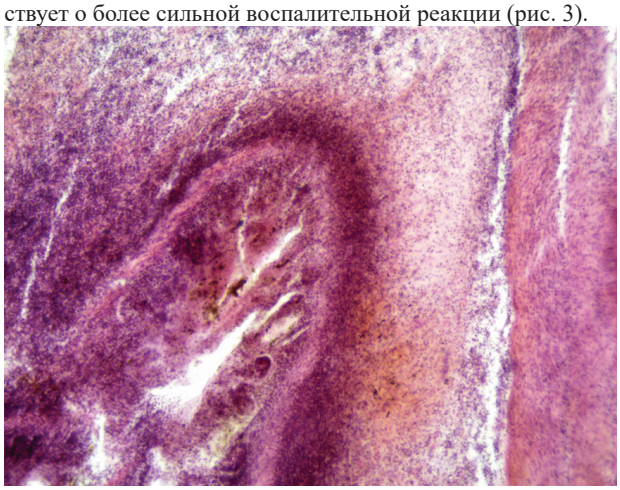

Рис. 3. Морфологическая картина анастомоза контрольной группы спустя 24 часа после операции. Окраска гематоксилином и эозином. Увеличение x160. Изъязвления слизистой, достигающих мышечного слоя, диффузная воспалительная инфильтрация стенки кишки, очаговый – некроз стенки кишки

Морфологическая картина анастомоза, выполненного традиционным способом, на 3 сутки характеризовалась полнокровием кровеносных и расширением лимфатических сосудов, выраженным отеком стенки кишки. Имеющиеся признаки гнойного воспаления прогрессировали. В зоне анастомоза отмечалась тотальная инфильтрация сегментоядерными лейкоцитами и миграция эозинофильных лейкоцитов в подслизистый и мышечный слои. Слизистая кишки в сравнении с первыми днями была без изъязвлений. В кровеносных сосудах определялись тромбы, в стенке кишки ячейки ограниченного некроза.

На третьи сутки в анастомозе, сформированном разра-

ботанным методом, гнойное воспаление было значительно менее выраженно.

Морфологические изменения в контрольной группе на 5 сутки характеризовались уменьшением отека стенки кишки, полнокровием кровеносных сосудов, снижением количества сегментоядерных лейкоцитов в стенке кишки. Отмечалось начало пролиферации соединительной ткани.

В опытной группе эти процессы были более выражены.

На 7 сутки после операции в стенке кишки, при формировании анастомоза традиционным способом, преобладали продуктивные изменения вокруг шовного материала, образовывались соединительнотканные волокна. Отек не выражен, лимфоидноклеточная инфильтрация незначительна (рис. 4).

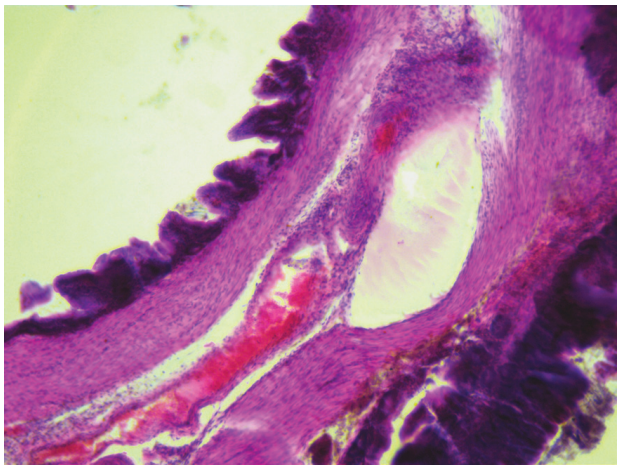

Рис. 4. Морфологическая картина анастомоза контрольной группы на 7 сутки после операции. Окраска гематоксилином и эозином. Увеличение х160. Продуктивные изменения вокруг шовного материала с образованием соединительнотканных волокон

По разработанной методике наблюдался отек подслизистого слоя и незначительная круглоклеточная инфильтрация стенки кишки (рис. 5).

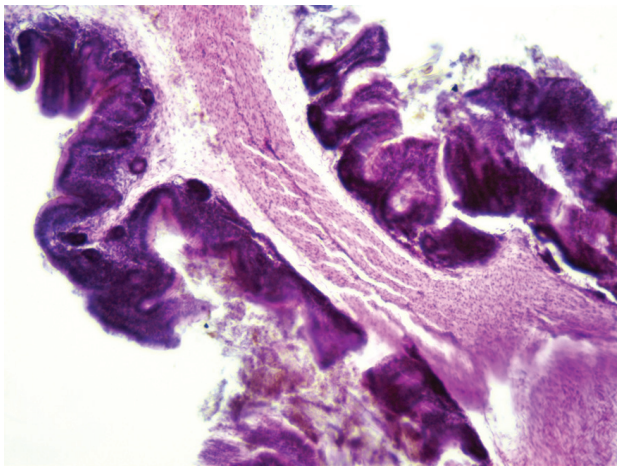

Рис. 5. Морфологическая картина анастомоза опытной группы на 7 сутки после операции. Окраска гематоксилином и эозином. Увеличение х160. Изъязвления слизистой оболочки, отек подслизистого слоя, незначительная круглоклеточная инфильтрация стенки кишки

Оригинальный способ формирования толстокишечного анастомоза позволил добиться биологической герметичности зоны анастомоза во все сроки раннего послеоперационного периода, тогда как в контрольной группе зона анастомоза становится стерильной при отсутствии нарушений заживления кишечного шва только с 5 суток.

Спустя сутки в обеих группах после операции выявлялось нарушение крово- и лимфооттока, что выражалось отеком подслизистой оболочки, скоплением в зоне анастомоза сегментоядерных лейкоцитов, ограничением участков некроза. При этом количество сегментоядерных лейкоцитов было значительно меньше в основной группе, что свидетельствовало о меньшей воспалительной реакции тканей. На третьи сутки признаки гнойного воспаления в контрольной группе прогрессировали, а в зоне анастомоза отмечена тотальная инфильтрация сегментоядерными лейкоцитами и миграция эозинофильных лейкоцитов в подслизистый и мышечный слои. В этот же срок в основной группе воспалительные явления были значительно менее выражены. С 5 суток в обеих группах уменьшался отек стенки кишки, полнокровие сосудов, снижалось количество сегментоядерных лейкоцитов в стенке кишки и начиналась пролиферация соединительной ткани. Эти процессы более выражены в группе, где применена оригинальная методика формирования ТКА. Эта тенденция сохранялась до 7 суток: воспалительные явления регрессировали в основной группе значительно быстрее. Таким образом, проведенное гистологическое исследование также подтвердило эффективность разработанного способа формирования толстокишечного анастомоза.

Формирование ТКА оригинальным способом позволило значительно улучшить течение раннего послеоперационного периода, что подтверждено проведенными исследованиями: оценкой механической прочности, биологической герметичности, сравнительными морфологическими характеристиками.

Абсолютные и средние показатели механической прочности ТКА у животных опытной группы были выше таковых в контрольной. Механическая прочность разработанного анастомоза характеризовалась более высокими показателями в сравнении с традиционным двухрядным анастомозом в контрольной группе.

Оригинальный способ формирования ТКА позволил добиться биологической герметичности зоны анастомоза во все сроки раннего послеоперационного периода, тогда как в контрольной группе зона анастомоза становится стерильной при отсутствии нарушений заживления кишечного шва только с 5 суток.

Морфологическая оценка по основным показателям - макроскопическая сравнительная характеристика, микроскопический анализ, подтвердила более эффективное заживление ран в основной группе.

При сравнительной макроскопической оценке ТКА в первые сутки различий не обнаружено. Одинаково выражена воспалительная реакция тканей, как следствие операционной травмы, которая представлена гиперемией, отеком, сосудистой реакцией и наличием небольшого количества серозного выпота в брюшной полости. К третьим суткам воспалительные явления нарастали, при этом у 1 животного при применении традиционного шва развилась несостоятельность кишечного анастомоза. В основной группе осложнений не отмечено. На пятые сутки воспалительные явления начинали регрессировать в обеих группах. Еще у

1 животного контрольной группы развилась несостоятельность анастомоза. При применении оригинальной методики несостоятельности не отмечено. На 7 сутки воспалительные явления в сравниваемых группах регрессировали, восстанавливалась кишечная проходимость в контрольной группе.

Таким образом, сравнительная макроскопическая клиническая оценка показала, что воспалительные явления при применении оригинальной методики купируются, в среднем, на 3-5 сутки, в то время как при применении традиционного способа сохраняются до 7 суток и носят более выраженный характер, сопровождаясь кишечным парезом и несостоятельностью ТКА (2 животных). При применении оригинальной методики формирования анастомоза послеоперационный период протекал более гладко, без вышеперечисленных осложнений.

Выводы. Механическая прочность однорядного ручного внутриузлового толстокишечного шва атравматической нитью 4/0 без прошивания слизистой прогрессивно выше на 66,3-85,4%, соответственно, на первых и седьмых сутках наблюдений в сравнению с традиционным двухрядным швом.

Формирование однорядного толстокишечного шва позволило добиться биологической герметичности зоны анастомоза во все сроки раннего послеоперационного периода, тогда как при использовании двухрядного шва зона анастомоза становится стерильной при отсутствии нарушений заживления кишечного шва только с 5 суток.

Морфологически картина характеризовалась воспалительными явлениями в зоне анастомоза при использовании оригинальной методики, которые купировались на 3-5 сутки, а при традиционном способе воспалительные явления сохранялись до 7 суток, сопровождаясь парезом сосудов стенки кишки, стазом крови и тромбами, с ячейками некрозов слизистой на 3 и 5 сутки наблюдения.

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SUMMARY

BIOLOGICAL HERMETICITY, MECHANICAL STRENGTH AND MORPHOLOGICAL CHARACTERISTICS OF ONE-ROW AND TWO-ROW COLON ANASTOMOSES

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Aim - comparison of biological hermeticity, mechanical strength and differences in morphological characteristics of one-row and two-row colon anastomoses.

20 animals were used in the experiment. Rabbits of both sexes aged from 8 months to 1.5 years and weighing from 1.5 to 2.6 kg were used as experimental animals. The animals were divided into experimental and control groups. In the experimental group we used the developed technique of one-row colon anastomosis (CA) formation, in the control group - the traditional two-row CA. Assessment of mechanical strength was performed by using the original method of pneumopression of colon segment with the anastomosis. The biological hermeticity was assessed by culturing flushing water from the anastomosis line to growth medium. The morphological picture was evaluated by microscopy of histological samples from the anastomosis line.

The mechanical strength of the one-row anastomosis, com-

pared with the traditional two-row, was higher at each stage of the study, on the first day by 66.3%, the third - 87.6%, the fifth - 76.1%, the seventh - 85.4%. The formation of a one-row CA allowed to achieve biological hermeticity of the anastomosis area in all periods of the early postoperative period, and when using a double-row suture, the anastomosis area became sterile only from 5 day. Morphologically, the picture was characterized by inflammatory processes in the anastomosis area when using the original technique, which were stopped in 3-5 days, and in the control group they persisted for up to 7 days, accompanied by vascular paresis of the intestinal wall, blood stasis and blood clots, with zones of mucosal necrosis at 3 and 5 day of observation.

Keywords: colon anastomosis, intra-colonic pressure, anastomotic leakage.

РЕЗЮМЕ

БИОЛОГИЧЕСКАЯ ГЕРМЕТИЧНОСТЬ, МЕХАНИЧЕСКАЯ ПРОЧНОСТЬ И МОРФОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ ОДНОРЯДНОГО И ДВУХРЯДНОГО ТОЛСТОКИШЕЧНОГО ШВА

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Цель исследования - сравнение биологической герметичности, механической прочности и различий морфологических характеристик однорядного и двухрядного толстокишечного шва.

В эксперименте использованы 20 кроликов обоих полов в возрасте от 8 месяцев до 1,5 года, весом от 1,5 до 2,6 кг. Животные разделены на 2 группы – опытную и контрольную. В опытной группе использовали разработанную методику формирования толстокишечных анастомозов (ТКА), в контрольной – традиционный двухрядный узловой шов. Оценку механической прочности определяли с помощью оригинальной методики пневмопрессии сегмента толстой кишки с анастомозом. Степень биологической герметичности определяли методом посева промывных вод с линии анастомоза на питательные среды. Морфологическую картину оценивали с помощью микроскопии гистологических образцов с линии анастомоза.

Механическая прочность однорядного ручного анастомоза в сравнении с традиционным двухрядным была выше на каждом этапе исследования: в первые сутки на 66,3%, на третьи – 87,6%, пятые – 76,1%, седьмые – 85,4%. Формирование однорядного толстокишечного шва позволило добиться биологической герметичности зоны анастомоза во все сроки раннего послеоперационного периода, а при использовании двухрядного шва зона анастомоза становится стерильной только с 5 суток. Морфологически картина при использовании оригинальной методики характеризовалась воспалительными явлениями в зоне анастомоза, которые купировались на 3-5 сутки, а при традиционном способе они сохранялись до 7 суток, сопровождаясь парезом сосудов стенки кишки, стазом крови и тромбами, с ячейками некрозов слизистой на 3 и 5 сутки наблюдения.

რეზიუმე

მსხვილი ნაწლავის ერთ- და ორრიგიანი ნაკერების ბიოლოგიური ჰერმეტულობა, მექანიკური გამძლეობა და მორფოლოგიური მახასიათებლები

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კვლევის მიზანს წარმოადგენდა მსხვილი ნაწლავის ერთ- და ორრიგიანი ნაკერების ბიოლოგიური ჰერმეტულობის, მექანიკური გამძლეობის და მორფოლოგიური მახასიათებლების განსხვავებათა შედარება.

ექსპერიმენტულ კვლევაში გამოყენებული იყო 8 თვიდან 1,5 წლამდე ასაკის, 1,5-2,6 კგ წონის ორივე სქესის 20 ბოცვერი. ცხოველები დაიყო ორ ჯგუფად – საცდელი და საკონტროლო. საცდელ ჯგუფში გამოყენებული იყო მსხვილი ნაწლავის ანასტომოზის ფორმირების შემუშავებული მეთოდიკა – ტრადიციული ორრიგიანი კვანძოვანი ნაკერი. მექანიკური გამძლეობა განისაზღვრებოდა მსხვილი ნაწლავის ანასტომოზიანი სეგმენტის პნევმოპრესიის ორიგინალური მეთოდიკის საშუალებით. ბიოლოგიური ჰერმეტულობა განისაზღვრებოდა ანასტომოზის ხაზიდან ჩარეცხილი წყლების დათესვით საკვებ ნიადაგებზე. მორფოლოგიური სურათი ფასდებოდა ანასტომოზის ხაზიდან აღებული ჰისტოლოგიური ნიმუშების მიკროსკოპიით.

ხელის ერთრიგიანი ანასტომოზის მექანიკური გამძლეობა,ტრადიციულ ორრიგიანთან შედარებით,კვლევის ყველა ეტაპზე იყო მეტი: პირველ დღეს – 66,3%-ით, მესამე დღეს – 87,6%-ით, მეხუთეზე – 76,1%-ით, მეშვიდეზე – 85,4%-ით. მსხვილი ნაწლავის ერთრიგიანმა ნაკერმა შესაძლებელი გახადა ანასტომოზის ზონის ბიოლოგიური ჰერმეტულობის მიღწევა ადრეული ოპერაციის შემდგომი პერიოდის ყველა ვადაზე, ხოლო ორრიგიანი ნაკერის გამოყენების შემთხვევაში ნაკერის ზონა სტერილური ხდება მხოლოდ მეხუთე დღეს.

ორიგინალური მეთოდიკის გამოყენების შემთხვევაში მორფოლოგიური სურათი ხასიათდებოდა ანთებითი მოვლენებით ანასტომოზის ზონაში, რაც კუპირდებოდა მე-3-5 დღეს; ტრადიციული ხერხის გამოყენებისას კი ანთებითი მოვლენები შენარჩუნდებოდა 7 დღემდე, რასაც თან ახლდა ნაწლავის კედლის სისხლძარღვების პარეზი, სისხლის სტაზი თრომბებით, ნეკროზის კერები ლორწოვანზე დაკვირვების მე-3 და მე-5 დღეს.

ЦИФРОВОЙ ТОМОСИНТЕЗ В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ: ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ В КОНТЕКСТЕ МИРОВОГО ОПЫТА (ОБЗОР)

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Физические явления, лежащие в основе применяемых в настоящее время методов лучевой диагностики, используют в медицинской практике более 40 лет, однако по сей день не удалось достичь междисциплинарного консенсуса по вопросу наиболее целесообразного их использования для решения прикладных диагностических задач в педиатрии. По мере совершенствования службы лучевой диагностики в РФ и накопления доказательных данных диагностический принцип «от простого к сложному», т.е. от доступных и относительно простых исследований к более трудоёмким и затратным, уступает место алгоритмизации обследования с учётом предварительного диагноза. Внедрение подобного подхода в педиатрическую практику позволяет сократить продолжительность обследования, минимизировать лучевую нагрузку на пациентов и должен быть постепенно закреплён в клинических рекомендациях. В настоящее время острая потребность в алгоритмизации диагностического этапа медицинской помощи связана и с ограничениями, вызванными пандемией COVID-19 (лимитированность ресурсов лечебно-профилактического учреждения - ЛПУ, перегруженность медицинских работников, необходимость соблюдения карантинных мероприятий).

Литературный обзор посвящён клиническим возможностям применения одного из низкодозовых вариантов визуализации в лучевой диагностике — методики ТС, применительно к особенностям педиатрической практики.

Характеристика методики ТС. Для лучевых снимков, сформированных проекционно (рентгенография, рентгеноскопия, ангиография, плоскостная сцинтиграфия), характерен так называемый суммационный эффект, представляющий собой наслоение изображений различных органов и тканей, расположенных вдоль прохождения пучка рентгеновского излучения. На рентгенограмме органов грудной клетки в прямой проекции позвоночный столб и медиальные сегменты лёгочной ткани у детей частично прикрыты тенью сердца, вилочковой железы и сосудистого пучка, что затрудняет распознавание и уточнение локализации патологических изменений, не позволяет исключить их маскировку за рентгенографической тенью других органов.

Проблема недостаточной проекционной визуализации на фоне суммационного эффекта может быть отчасти решена благодаря ТС — современной методике рентгенологической диагностики, позволяющей получать определённое количество послойных изображений объёмной реконструкцией срезов [1,2]. Технология позволяет за один проход рентгеновской трубки обследовать обширную анатомическую зону, диагностировать трудноразличимые при цифровой рентгенографии патологические изменения без потери качества получаемых изображений, что особенно актуально в педиатрической практике. В определённых клинических ситуациях такой подход даёт возможность получить необходимые данные без проведения мультиспиральной компьютерной томографии (МСКТ), благодаря чему лучевая нагрузка может быть снижена, по разным данным, в 7-10,5 раз [3,4].

К настоящему времени в РФ широко распространены цифровые рентгеновские аппараты отечественного и зарубежного производства, по пространственному разрешению, динамическому диапазону и контрастной чувствительности значительно превосходящие аналоговую методику. Данный класс аппаратов оснащён возможностью создания серии томограмм без суммационного эффекта с низкой лучевой нагрузкой [24]. В литературе описаны возможности и уточнено место методики ТС в диагностике заболеваний опорно-двигательной системы [5], органов грудной клетки [3,7]. Исследовательские работы, касающиеся применения ТС в пульмонологической практике, сосредоточены на ранней диагностике очаговых процессов [8,9] и интерстициальных болезнях лёгких [25], в том числе туберкулёзе [6], пневмонии (включая вызванную SARS-CoV-2) [13,18-20], а также для визуализации изменений, сформировавшихся вследствие хронических процессов (муковисцидоз, ХОБЛ). Тем не менее, для обследования пациентов детского возраста данную методику по сей день применяют весьма ограниченно.

Возможности ТС при обследовании костей и суставов. Методику ТС широко применяют для диагностики заболеваний опорно-двигательной системы, особенно патологических изменений в шейном отделе позвоночника, в том числе для оценки соотношения С1–С2. У детей раннего возраста в указанной области нередко возникает ротационный подвывих, рентгенологическая диагностика которого серьёзно затруднена необходимостью специальной укладки пациента (с открытым ртом) для устранения суммационного эффекта и проведения функциональных проб, что зачастую требует повторных снимков. При ТС возможно эффективное определение патологических изменений в С1–С2 на единственной серии томограмм без укладки с открытым ртом [5].

Чёткость послойной визуализации костно-трабекулярных структур при ТС позволяет оценивать структурные и статические изменения во всех отделах позвоночника (склерозирование и узурация замыкательных пластин, неравномерное снижение высоты межпозвонковых дисков, минимальные краевые костные заострения). Ранняя диагностика остеохондропатий значима при планировании консервативно-восстановительного лечения иособенно при разработке режима занятий спортом у детей и подростков. Для исследования грудного и поясничного отделов позвоночника наиболее информативны томограммы в боковой проекции.

Послойная визуализация сложных анатомических структур, входящих в состав скелета стопы и кисти, имеет особенную значимость в педиатрической ортопедии и травматологии с учётом широкой вариабельности возрастной нормы и сроков оссификации костей. Применение ТС способствует ранней диагностике патологических изменений дистальных сегментов конечностей без применения множественных рентгенографических укладок и МСКТ.

В ряде случаев методика ТС позволяет получить необходимую информацию при обследовании пациентов

детского возраста с подозрением на доброкачественные опухоли и опухолеподобные заболевания костей [5]. Преимущества ТС над проекционной рентгенографией выражены ярче, если область, подлежащая исследованию, содержит металлические элементы (скобы, импланты, спицы, пластины) [10].

Возможности ТС при обследовании органов грудной клетки. Для детального изучения патологических изменений органов грудной клетки, невсегда обнаруживаемых при цифровой рентгенографии вследствие суммационного эффекта, методом выбора признана МСКТ. Эта методика позволяет детально оценить анатомические и патологические изменения лёгких, плевры, костных элементов и органов средостения. Подобная диагностическая тактика может быть ограничена относительно высокой лучевой нагрузкой [11] и потребностью в седации у детей раннего возраста (с целью обеспечения неподвижности на время исследования). Применение ТС, как правило, позволяет удовлетворительно визуализировать область, интересующую клиницист, даже на фоне движений бодрствующего пациента. Это особенно значимо при выполнении исследования у детей, неспособных произвольно задержать дыхание ввиду раннего возраста или в связи с тяжестью состояния. Подобная клиническая ситуация была смоделирована Rakowski J.T. (2018) с использованием 4D-модели ТС лёгких на фоне движения грудной клетки. Автором был сделан вывод о возможности получения качественного изображения путём технического и программного уменьшения влияния динамических и анатомических артефактов [12].

При ТС тени грудино-ключично-сосцевидных, лестничных, больших и малых грудных мышц, а также молочных желёз и сосков, понижающие прозрачность лёгочных полей и способные имитировать патологический процесс при стандартном рентгенографическом обследовании органов грудной клетки в прямой проекции, практически не влияют на оценку характеристик органов средостения и лёгочной ткани. Учитывая значимую вариабельность анатомических характеристик молочных желёз (величина, расположение и рентгенологическая плотность), анализ серии томограмм обеспечивает убедительное преимущество при обследовании органов грудной клетки пациенток подросткового возраста [3].

Благодаря отсутствию суммационного эффекта диагностическая ценность ТС для выявления интерстициальных болезней лёгких достоверно выше, чем при стандартной рентгенографии грудной клетки ($p<0,05$). По данным контролируемого исследования чувствительность ТС в определении указанной группы состояний составила 83,3%, а отрицательная прогностическая ценность — 89% (рентгенография — 43,9% и 70,9%, соответственно). Межэкспертная согласованность и достоверность диагноза, сформулированного с учётом результатов ТС, значительно лучше, чем у рентгенографии ($p <0,001$). По мнению авторов, преимущества ТС перед рентгенографией позволяют рассматривать вопрос об использовании методики в качестве стартовой в группе пациентов с подозрением на интерстициальные болезни лёгких [25,26].

В ходе некоторых исследований на основе комплексного клинико-рентгеноморфологического обследования 170 пациентов с очагово-инфильтративными изменениями на рентгенограммах, позволившими заподозрить туберкулёз лёгких, диагноз был подтверждён у 121 пациента. При этом чувствительность ТС в выявлении специфических патологических изменений составила 74,9% (показатель больше, чем при рентгенографии, на 17,7% и меньше, чем при МСКТ, на 18,6%). Авторы делают вывод о том, что использование ТС в качестве уточняющей методики целесообразно для обследования пациентов с подозрением на туберкулёз лёгких, поскольку позволяет выявлять, достоверно оценивать распространённость и детально характеризовать очагово-инфильтративные изменения в ткани органа [6].

Согласно рекомендациям, сформулированным в Национальном руководстве Соединенного Королевства и Соединенных Штатов по диагностике и лечению внебольничной пневмонии у детей, «рентгенологам следует улучшить рентгенографическую диагностику пневмонии, достичь терминологического консенсуса и менять метод визуализации, если это повышает точность или надёжность» [13]. В отечественных клинических рекомендациях, разработанных Российским респираторным обществом и Межрегиональной ассоциацией по клинической микробиологии и антимикробной химиотерапии (2018) [18], сделан акцент на том, что «у части больных рентгенологическая картина не типична или клинические проявления, сходные с пневмонией, обусловлены другим патологическим процессом. В этих случаях полезными могут быть другие методы лучевой диагностики».

На роль обсуждаемой альтернативы, помимо УЗИ лёгких у детей раннего возраста и МСКТ соответствующего сегмента тела, может претендовать в том числе и ТС органов грудной клетки [14]. По данным Боголеповой Н.Н. и соавт. [20], впервые давших оценку роли методики в детском ЛПУ по итогам анализа результатов 57 исследований, информативность ТС выше, чем при цифровой рентгенографии и линейной томографии, но ниже, чем при МСКТ. В то же время низкая доза облучения при ТС, сопоставимая с латеральной рентгенографией лёгких, подтверждает целесообразность применения методики в педиатрической практике.

В исследовании, описанном В.А. Нечаевым и А.Ю. Васильевым [19], при обследовании 128 пациентов показано, что ТС превосходит цифровую рентгенографию в обнаружении многих рентгеносемиотических признаков, в связи с чем может быть полезен для повышения эффективности диагностики. Несмотря на то, что ТС несколько уступает МСКТ в точности распознавания симптомов, в 67,2% наблюдений включение методики в план обследования позволило получить дополнительную информацию. Заслуживает внимания то, что у 39,8% обследованных данные, полученные при ТС, оказались клинически значимыми и повлияли на дальнейшую тактику ведения этих пациентов.

Особенности использования ТС при обследовании детей. Одно из очевидных преимуществ ТС над другими вариантами лучевой диагностики с возможностью объёмной реконструкции изображения состоит в достоверном уменьшении лучевой нагрузки. В клинической практике это позволяет повторно обследовать пациента для оценки эффективности проводимого лечения в динамике. Vult von Steyern K. и соавт. [15] по итогам ТС-обследования 38 детей с муковисцидозом и 36 детей с узловыми новообразованиями лёгких рассчитали усреднённые параметры эффективной дозы как ориентировочные для обследования детей. Ими выполнено всего 17 исследований в переднезадней проекции и 169 исследований в заднепередней проекции (40 мальчиков и 34 девочки от 7 до 20 лет).

В расчётах авторы использовали данные о конверсии ТС грудной клетки у детей с поправкой на возраст; средняя задняя эффективная доза на одну процедуру составила 0,17

мЗв. Предложены к использованию упрощённые коэффициенты пересчета на возраст пациента:

- 0,6 мЗв Гр см$^{-2}$ у 8–10-летних;
- 0,4 мЗв Гр см$^{-2}$ у 11–14-летних;
- 0,3 мЗв Гр см$^{-2}$у 15–17-летних детей.

При таком варианте определения расчётная средняя задняя эффективная доза составила 0,15 мЗв. Погрешность в случае использования перечисленных упрощённых коэффициентов, адаптированных для педиатрической практики, авторы называют незначительной.

По данным Blum A. и соавт. (2018), эффективная доза облучения для пациента при выполнении ТС превышает показатель при цифровой рентгенографии с плоской детекторной панелью не более чем в 2–3 раза [10]. Исследвоания, выполненные в 2014–2017 гг., демонстрируют резерв дальнейшего снижения лучевой нагрузки без потери качества получаемого изображения [21,22]. Данный факт особенно значим при сопоставлении клинической ценности методики ТС и новых протоколов МСКТ с очень низкой дозой: например, использование ТС для оценки динамики восстановления запястья после травматического повреждения позволило добиться 28-кратного снижения дозы облучения[23].

Выполнение ТС у детей возможно в положении стоя или лёжа в зависимости от исследуемой области, возраста, индивидуальных физических особенностей и тяжести состояния пациента. Для исследования позвоночника, органов грудной клетки, в том числе с функциональными пробами следует отдавать предпочтение исследованию пациента в положении стоя, ТС костей конечностей целесообразно выполнять в положении лёжа. В случае, если ребёнок ввиду возраста или тяжести состояния не может самостоятельно поддерживать необходимое положение тела, экранирующий фартук надевает ассистирующий (удерживающий ребёнка в нужном положении) законный представитель.При необходимости обследовать в положении стоя ребёнка ниже 120 см целесообразно применять устойчивые подставки с регулируемой высотой; в этом случае ассистирующий при исследовании взрослый фиксирует ребёнка на подставке во избежание падения [2].

Нормативная база применения ТС в Российской Федерации. Авторство и правообладание на изобретение «Способ проведения томосинтеза органов грудной полости» принадлежат Ратобыльскому Г.В. и Никитину М.М. Выполнение ТС пациентам детского возраста имеет технические и организационные особенности, подробно описанные в немногочисленных публикациях [6].

В настоящее время методика ТС не фигурирует среди основных или дополнительных методов обследования, рекомендуемых методическими [1] или клиническими рекомендациями [18,27,28], регламентирующими педиатрическую практику на территории Российской Федерации. Проведение ТС возможно при выполнении одного из следующих условий:

а — проведение ТС запланировано лечащим врачом (с оформлением соответствующих показаний к исследованию в карте амбулаторного пациента или истории болезни);

б — проведение ТС рекомендовано врачом лучевой диагностики в рамках дообследования (о чём содержатся сведения в протоколе ранее выполненного исследования);

в — конкретная клиническая ситуация соответствует критериям включения в исследовательскую работу, имеющую положительное заключение Межвузовского комитета по этике, а от законных представителей несовершеннолетнего (либо самого несовершеннолетнего старше 15 лет), получивших необходимые разъяснения, получено информированное добровольное согласие на проведение ТС [2]. При этом к медицинской документации пациента должны быть приобщены копия заключения Межвузовского комитета по этике, копия информированного добровольного согласия, электронный носитель с неанонимизированной записью исследования и копия протокола описания.

Перспективы внедрения диагностических алгоритмов с использованием ТС. В ретроспективном наблюдательном исследовании, посвящённом оценке деятельности отделения торакальной радиологии многопрофильного ЛПУ, установлено, что в перспективе ТС может частично заменить цифровую рентгенографию как менее информативную методику и МСКТ как высокодозовую. По мнению авторов, перспективы экспансивного внедрения ТС в алгоритмы диагностики могут снизить потребность в цифровой рентгенографии как минимум на 20% (преимущественно за счёт сокращения снимков в боковой проекции) и МСКТ на 25% [16].

Согласно опубликованным экспертным оценкам, широкое внедрение ТС в алгоритмы обследования органов грудной клетки у пациентов детского возраста (с учётом результатов рентгенографии) способно обеспечить клинициста необходимой информацией и снизить потребность в МСКТ на 70–80% [11,17].

Заключение. ТС представляет собой эффективную методику лучевой диагностики, позволяющую выявить либо уточнить характер патологических изменений костно-суставной системы или органов грудной клетки у детей старше 3 лет без потребности в седации и привлечения высокодозовых технологий. Требуется дальнейшее детальное изучение возможности применения ТС в следующих клинических ситуациях: необходимость дообследования при наличии очаговых теней в ткани лёгких, потребность в детальной визуализации пороков развития органов грудной клетки и других анатомических особенностей, подозрение на внебольничную пневмонию. По мере накопления данных доказательной медицины, подтверждающих целесообразность внедрения ТС в алгоритм обследования при тех или иных патологических состояниях, целесообразно выносить соответствующий вопрос на междисциплинарное обсуждение экспертных групп и профессиональных сообществ, регулярно пересматривающих клинические рекомендации по тем или иным состояниям.

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SUMMARY

DIGITAL TOMOSYNTHESIS IN PEDIATRIC PATIENTS: OPPORTUNITIES AND PROMISES (REVIEW)

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Digital tomosynthesis (TS) are modern methods of low-dose x-ray diagnostics, which allows to obtain a significant number of layered images with the possibility of volumetric image reconstruction. The technology makes it possible to analyze a vast anatomical zone in one pass of the x-ray tube, to diagnose difficult-to-distinguis pathological changes that are not visible in digital radiography without losing the quality of the images, which is especially important in pediatric practice.

The present literature data is devoted to the possibilities of using TS in the diagnosis of a wide range of diseases in children, as well as the prospects for further development of the methods to solve specific problems associated with the examination of children's patients.

Keywords: digital tomosynthesis, bones and joints diseases, interstitional lung diseases.

РЕЗЮМЕ

ЦИФРОВОЙ ТОМОСИНТЕЗ В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ: ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ В КОНТЕКСТЕ МИРОВОГО ОПЫТА (ОБЗОР)

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Цифровой томосинтез (ТС) представляет собой современную методику низкодозовой рентгенологической

диагностики, позволяющую получать значительное количество послойных снимков с последующей объёмной реконструкцией изображения. Применение ТС позволяет обследовать обширную анатомическую зону за один проход рентгеновской трубки, диагностировать трудноразличимые патологические изменения, невидимые при цифровой рентгенографии, без потери качества получаемых изображений, что особенно актуально в педиатрической практике. Обзор литературных данных посвящён возможностям применения ТС в диагностике широкого спектра заболеваний у детей, а также перспективам дальнейшего развития методики для решения специфических задач, связанных с обследованием пациентов детского возраста.

რეზიუმე

ციფრული ტომოსინთეზი პედიატრიულ პრაქტიკაში: შესაძლებლობები და პერსპექტივები მსოფლიო გამოცდილების კონტექსტში (მიმოხილვა)

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ციფრული ტომოსინთეზი წარმოადგენს დაბალდოზიანი რენტგენოლოგიური დიაგნოსტიკის თანამედროვე მეთოდიკას, რომელიც იძლევა შრეობრივი სურათების მნიშვნელოვანი რაოდენობის მიღების საშუალებას, გამოსახულების შემდგომი მოცულობითი რეკონსტრუქციით. ციფრული ტომოსინთეზის გამოყენება რენტგენის მილის ერთი ნაკადის გასვლით იძლევა ფართო ანატომიური ზონის გამოკვლევის, ძნელად გარჩევადი, ციფრული რენტგენოგრაფიით უხილავი პათოლოგიური ცვლილებების დიაგნოსტიკის საშუალებას, ამასთან - მიღებული გამოსახულების ხარისხის დაკარგვის გარეშე, რაც განსაკუთრებით აქტუალურია პედიატრიულ პრაქტიკაში.

ლიტერატურის მონაცემების მიმოხილვა ეძღვნება ციფრული ტომოსინთეზის გამოყენების შესაძლებლობას ბავშვთა დაავადებების ფართო სპექტრის დიაგნოსტიკაში, ასევე, მეთოდიკის შემდგომი განვითარების პერსპექტივებს ბავშვთა ასაკის პაციენტების გამოკვლევასთან დაკავშირებული სპეციფიკური ამოცანების გადაჭრაში.

GERHARD HANSEN VS. ALBERT NEISSER: PRIORITY FOR THE INVENTION OF MYCOBACTERIUM LEPRAE AND PROBLEMS OF BIOETHICS

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According to the WHO definition, leprosy, also known as Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae. The disease mainly affects the skin, the peripheral nerves, mucosal surfaces of the upper respiratory tract and the eyes [23]. At the present stage, leprosy belongs to the conditionally eliminated diseases, however, every year there are cases of infection with this disease [20].

A vivid indication that leprosy has been a threat to humans since ancient times is that the biblical texts contain many speculations about this disease, in particular, the thirteenth chapter of Leviticus, which is part of the Pentateuch (Torah), gives a very detailed description of leprosy with an attempt, so to speak, to diagnose differentiall . Thus, if a patient has depigmentation of hair and "deep" ulcers, the priest must "diagnose" leprosy and declare the patient unclean [17, 13:3]. In seven days, the priest can distinguish leprosy from herpes or psoriasis [17, 13:6; 17, 13:31]. A rather thorough analysis of skin diseases in sacred texts was made by the Brazilian researchers R. A. M. Frutuoso, G. R. D Ferreira, S. B. Frutuoso [6], the Russian researchers O. Terletsky and G. Grigoriev [22], as well as the Uzbek scientists I. Karomatov and H. Gulyamov. [14]. However, the interpretation of its etiology and pathogenesis was far from scientific, because it was believed that this disease is a divine punishment for sin and a demonstration of God's wrath to mortals. A careful reading of this section of the Torah confirms the thesis that the people of the Ancient East often confused leprosy with other skin diseases, there are a large number of synonyms that denote various morphological elements of dermatological manifestations of diseases such as scleroderma, eczema, vitiligo, mycosis, herpes, psoriasis [4].

The disease, whose complications for thousands of years killed tens of thousands of patients who were feared and brand-

ed, isolated and expelled from society, remained unexplored until the 1870s and only during the rapid development of microbiology there was a real breakthrough in the diagnosis, treatment and prevention of leprosy. An invaluable contribution to these issues belongs to the Norwegian microbiologist and leprologist, Gerhard Hansen, and the German doctor, microbiologist Albert Neisser, jokingly referred to by his students as the "father of Honococcus". The aim of the research is to study the biographies of Gerhard Hansen and Albert Neisser in the comparative aspect.

Material and methods. The general scientific methods, including analysis and synthesis, as well as biographical and comparative-biographical methods were used in the study. The research material relied on the biographies of Gerhard Hansen and Albert Neisser.

Results and discussion. Gerhard Henrik Armauer Hansen was the Norwegian bacteriologist who discovered the leprosy agent – Mycobacterium leprae (bacillus Hansen) and refuted the theory of heredity of the disease. Gerhard Hansen was born on July 29, 1841 in Bergen in a large family – the boy was the eighth child out of 15 [7]. He studied medicine at the Royal University of Frederick (now Oslo University). He obtained his scientific degree in 1866. For the next two years, G. Hansen worked at the National Hospital of Christiania, as well as in one of fis - ing communities of the Lofoten Islands. In 1868, G. Hansen returned to his hometown, which at that time was the focus for the Norwegian studies of leprosy, and became an assistant to the famous specialist-leprologist D. Danielssen (Daniel Cornelius Danielssen, 1815-1894) [1], who in 1847 along with dermatologist C. Boeck (Carl Wilhelm Boeck 1808-1875) co-authored a study on leprosy, which played a significant role in the research and treatment of this disease.

Interesting is the fact that D. Danielssen conducted experiments in vivo: he rubbed in his own scratches, or his subordinates, as well as volunteer patients with other diseases, the pus from leprous nodes in patients with leprosy. However, the infection did not occur, although these experiments did not go without a trace for D. Danielssen: he contracted tuberculosis of bones, infected his wife and four children who eventually all died, while D. Danielssen himself lived to almost 80 years of age.

If D. Danielssen mistakenly believed that leprosy was a hereditary disease [1], then G. Hansen, who travelled extensively around Norway and assisted patients, put forward the revolutionary hypothesis at that time that leprosy was not a hereditary disease but a contagious bacterial disease with a chronic course. Contrary to D. Danielssen's scientific authority, G. Hansen was able to maintain excellent personal relationships with him, and the fact that the organized preventive measures provided a significant reduction in the number of new infections only confirmed his bold assumptions. This was the impetus for G. Hansen to begin his own experimental and epidemiological study. In his first work, dated 1869, G. Hansen used the term "infectious substance" and described leprosy changes. However, poor material equipment did not contribute to the proper formulation of the data obtained experimentally.

In 1870, G. Hansen won a grant and was able to improve his qualification in histopathology in Bonn, where he was supervised by Max Johann Sigismund Schultze, 1825-1974 - a prominent German anatomist, zoologist and histologist. The Franco-Prussian War, which began in the same year, did not contribute to advanced training, so G. Hansen moved to study in Vienna [7; 8, p. 297]. In early 1873, G. Hansen became engaged to the daughter of his mentor D. Danielssen Fanny (Stephanie) (who, like other children of D. Danielssen, would soon die of pulmonary tuberculosis) [1; 7; 12]. At the wedding, the newly wedded couple was presented with a new modern microscope, and G. Hansen zealously began to examine the brown mass characteristic of lepromatous nodes. The result was rapid: on February 28, 1873, he found small sticks that were stacked in equal rows [13]. The scientist presented the results of his research in a work that became epoch-making and a year later was published in the major Norwegian scientific journal, later was translated into English as *Investigations Concerning the Etiology of Leprosy*, and in which he discovered the sticks that were tentatively called "rods" [1].

As R.K. Kannan points out [13], the results of G. Hansen's discovery were ahead of his time: some colleagues were quite skeptical, arguing that he saw the sticks, but whether they cause the disease is unknown, some scholars mocked the scientist, and others opposed him in all possible ways. Despite the fact that G. Hansen did not know how to prove the authenticity of his invention, his experiments aroused considerable interest among many researchers from other countries. For example, it is known that a Swedish veterinarian Edlund tried to appropriate (though unsuccessfully) G. Hansen's invention.

A similar situation occurred with the colleague of the microbiologist-innovator, the future Nobel Prize winner Robert Koch (Robert Koch, 1843-1910) – dermatologist and venereologist A. Neisser (Albert Ludwig Sigesmund Neisser, 1855-1916), already famous at that time for discovering the causative agent of gonorrhea, named Neisseria gonorrhoeae.

In 1879, A. Neisser came to Norway, and G. Hansen arranged for an honorary guest for a two-month trip around leprosaries, showed him 600 patients and provided a considerable amount of biological preparations. After returning to Breslau, A. Neisser began to stain bacteria previously detected by G. Hansen and hypothesized that these bacteria were infected by agents of leprosy, thereby declaring the priority of opening the leprosy pathogen [15]. Meanwhile, Koch informed G. Hansen of the success of his subordinate and introduced him to a new method by which the sample of infected tissue had to be impregnated with fuchsin for a day, after which the bacilli of the leprosy became bright red and clearly differ ntiated. It is natural that G. Hansen decided to prove his priority for the discovery, and in 1880 he managed to stain the bacteria of leprosy.

As both G. Hansen himself, and his father-in-law and mentor D. Danielssen were resistant to leprosy, according to E. Koch's suggestion, it was decided to further infect an already sick person in order to obtain biological material to confirm G. Hansen's hypothesis. On November 3, 1879, G. Hansen, as chief leprologist, summoned a 33-year-old leprosy patient Kari Spiessen, who had been ill with leprosy since the age of 16, and, without her voluntary consent, wanted to incise her cornea with an infected scalpel. The patient was initially scared and refused, but Hansen's colleague reassured her and the woman agreed. When this story became widely known in the medical environment, G. Hansen's actions, despite the *pia desideria* of the researcher, were found to be incompatible with the high rank of a doctor, although, on the other hand, the evidence of the scientist's guilt was insufficien to conclude [8; 16]. By the King decree, G. Hansen was deprived of the right to treat patients and was put on trial, although he retained the position of chief leprologist on a social basis until his death [18].

Last but not least, the scandal was triggered by A. Neisser, who published his description of leprosy pathogen and said that although G. Hansen saw the microorganism, he could neither

stain it nor prove that it is a bacterium. In addition, A. Neisser referred to D. Danielssen, as if G. Hansen had not shown him his bacillus. These statements were aroused an attack of rage in D. Danielssen, who had collaborated and supported G. Hansen throughout his life [21]. In addition, G. Hansen received unprecedented support from all Norwegian doctors who defended the great Norwegian discovery: the Norwegian medical community, outraged by these events, insisted that G. Hansen submitted explanatory statements to the European scientific journals in English, German and French. During the trial of G. Hansen, held on May 31, 1880, each of the interrogated medical experts confirmed that G. Hansen acted in the interests of the motherland, medicine and science. Despite the fact that G. Hansen was deprived of the opportunity to treat patients, his authority in the scientific world remained unshakable: G. Hansen held many honorary positions, in particular, since 1874 he occupied the position of director of Bergen Museum of Natural History, was a member of medical unions, and co-founder of the Leprosy profile journal. At Berlin Congress of Leprologists, held in 1897, G. Hansen was recognized as a "famous man" for his brilliant discovery [16, p. 213], referred to by the Norwegians as "unique in Norwegian medicine" [11, p. 424]. G. Hansen died of a heart attack on February 12, 1912. Funeral service of a prominent scientist was held at the museum, which he headed for almost 40 years, and his ashes remain there to this day [10].

Ut supra, another iconic figure in the history of world leprology is Albert Ludwig Sigesmund Neisser, the German doctor, microbiologist, who was jokingly referred to by his students as "the father of gonococcus". A. Neisser was born on January 22, 1855, in the family of Doctor Moritz Neisser (1820-1896) in the small town of Schweidnitz (now the Polish town of Swidnica) near Breslau (modern Polish Wroclaw). The boy's mother died when he was just 1 year old, so he was raised by his stepmother. After graduating from St. Mary Magdalen High School, where his classmate was Paul Ehrlich, the future outstanding immunologist and bacteriologist, Nobel Prize winner in Physiology and Medicine (1854-1915), A. Neisser entered the University of Breslau, which was considered the top German university, and also studied at the University of Erlangen for one semester. In 1877, under the supervision of Michael Biermer (Michael Anton Biermer, 1827-1892), A. Neisser defended his thesis on echinococcosis and received his doctorate degree [19, p. 229].

A. Neisser planned to become a specialist in the field of internal diseases, but due to the fact that his scientific supervisor did not have a vacant position of an assistant, he accidentally got to the dermatological clinic of Heinrich Koebner (1838-1904) and received the position of an assistant of dermatologist Oscar Simon (1845-1892). It was while working at this clinic that 24-year-old A. Neisser discovered the causative agent of gonorrhea in 1879. A. Neisser examined 35 patients: 26 adult patients with typical purulent urethritis, seven clinical cases of neonatal infection, and two with ophthalmic manifestations. Initially, this pathogen was called "micrococcus", and in 1882 A. Neisser gave it another name – "gonococcus" [2], which was later changed to the modern one – Neisseria gonorrhoeae. This discovery was the start of his research career, of which he often jokingly said later: "What would I have been without the gonococcus?" [19, p. 230].

As noted above, in 1879 A. Neisser went to Norway, where the famous leprologist G. Hansen handed him tissue samples of patients with leprosy. After returning to Germany thanks to the latest technology at his disposal, A. Neisser identified the causative agent of this disease [11, p. 230]. However, this invention was accompanied by a high-profile international scandal, as A. Neisser declared his priority of the invention of the leprosy agent, although G. Hansen had done so before. Thanks to R. Koch's intervention, this situation was resolved quite diplomatically. In 1880, A. Neisser received the title of Associate Professor at Leipzig University, and two years later returned to Breslau at the age of 27 to take up the vacant post of his teacher, O. Simon, who died of cancer [19, p. 230].

Over the next three decades, A. Neisser made a brilliant career, not least made possible by the financial support of the all-powerful Prussian education and culture advisor Friedrich Althoff (1839-1908), who sponsored A. Neisser for 27 years. It is because of this support that the dermatological clinic was founded in Breslau in 1892, built by A. Neisser's project – a large, modern 95-seat building with laboratories equipped with state-of-the-art facilities, lecture halls, a zoo, a museum and a library. It is natural that this clinic has become a world-renowned research center.

A. Neisser is known not only as a researcher for gonorrhea, anthrax, actinomycosis, psoriasis, vitiligo, as a scientist who proved the tuberculous origin of lupus, but also, above all, as a scientist who made a significant contribution to the study of syphilis, which was, like leprosy, a huge medico-social problem for centuries.

A series of experimental studies on syphilis via inoculation conducted by A. Neiser led to a high-profile scandal, which, ironically, was similar to the scandal that at one time exploded around the name of another leprosy researcher, G. Hansen. A. Neisser was accused of introducing syphilitic serum without the consent of patients (these were four prostitutes aged from 17 to 20 years) [19, p. 231]. For this experiment, in 1900 A. Neisser was publicly fined 300 marks. However, neither his reputation, nor his medical license, or his further scientific career suffered a significant impact, as the German medical community supported the scientist [10] (unlike G. Hansen, who was deprived of the right to treat patients by the King's decree and was put to trial). It is worth noting that this scandal undoubtedly had a positive effect, as it was thanks to him that the first government decree was issued, according to which the subjects of experiments had to give informed consent to participate in clinical trials [3].

An important role in further studies of syphilis was played by scientific expeditions of A. Neisser (which he organized at his own expense) to the island of Java and to Botavia (the territory of modern Indonesia), where the Dutch military contingent was temporarily stationed, and many soldiers were ill with syphilis. These expeditions enabled the scientist to experimentally investigate the mechanisms of syphilis transmission, including from a monkey to a human being. A. Neisser has also made it into history as an active fighter for the prevention of sexually transmitted diseases through health education and informing the general public about measures to prevent sexually transmitted diseases and introducing rigid sanitary measures aimed at minimizing the spread of syphilis.

Interestingly, A. Neisser argued for the rigid regulation of prostitution and the strengthening of sanitary measures against the representatives of this profession. In 1899, A. Neisser co-founded the German Dermatological Union, and in 1902, the German Union against Sexually Transmitted Diseases, and he remained its secretary-general until his death. In 1883, A. Neisser married Toni Kauffmann, a descendant of a wealthy Jewish family who became a constant companion in the scientist's life [19, p. 231]. The death of his beloved wife in 1913 had a negative impact on the health of the scientist who had diabetes,

nephrolithiasis and cystitis for a long time. In addition, a few years before his death, A. Neisser unsuccessfully fell and broke his hip: he did not fully recover from this injury.

A. Neisser painfully survived the outbreak of World War I and as a patriot of Germany became a signatory to the so-called Manifesto 93 – "Aufruf an die Kulturwelt" ("To the Civilized World"), in which the prominent German figures of science and culture tried to whitewash and justify the war crimes of the Kaiser, committed during the first two months of World War I. In 1916, A. Neisser's health deteriorated sharply after he underwent the bladder removal at Berlin hospital. A. Neisser died of septicemia at the age of 62. He bequeathed his house to the city. In 1920, an art gallery was created in this house. In 1933, the building was seized by the Nazis and housed a hotel that was destroyed during World War II. Fortunately, A. Neisser's works, which were part of the museum funds, were saved by a doctor from Schweinfurt by the name of Brock, and now they are stored in the library of the famous clinic, built by A. Neisser in his time.

Conclusions. Comparative analysis of biographies of the prominent microbiologists G. Hansen and A. Neisser showed that despite the desire to serve science and humanity, adherence to the rules of bioethics, as well as human morality should remain an integral part of the activity of any scientist, a physician in particular. The timely publication of scientific achievements is a significant moment in the event of disputed questions about the priority of a scientific discover .

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SUMMARY

GERHARD HANSEN VS. ALBERT NEISSER: PRIORITY FOR THE INVENTION OF MYCOBACTERIUM LEPRAE AND PROBLEMS OF BIOETHICS

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The article is interdisciplinary in nature and covers a wide range of issues in the history of medicine, morality and bioethics. Biographies of the Norwegian microbiologist G. Hansen and the German doctor, biologist, syphilologist A. Neisser are presented. The main attention is focused on the scientific achievements of these researchers in terms of infectious diseases and leprosy in particular. The authors focused not only on the significance of scientific discoveries, but also tried to show that any scientist, even an outstanding one, remains a person with his/her unique character, personal life and friendships, authority in the scientific community and mistakes, desire to gain fame and recognition. The main focus is on the scientific achievements of these researchers in the study of infectious diseases and leprosy in particular. The conflict over the priority for discovery of the leprosy pathogen has been highlighted. Attention is given

to the conflict regarding the priority in discovery of the causative agent of leprosy. The authors compared the impact of the international scientific scandal on the priority for the discovery of Mycobacterium leprae, which involved virtually the entire scientific community of Europe at the time, on both scientists. It has been shown that most scientists unambiguously sided with G. Hansen, who was not only the author of the revolutionary hypothesis of the contagious and bacterial nature of leprosy at the time, but also the pioneer of the causative agent of this disease, as evidenced by the synonymous name Mycobacterium leprae – bacillus Hansen. Nevertheless, for a prominent scientist, the consequences of an unethical experiment on intentional additional infection of a patient became quite tragic, since he lost his license to practice medicine, and was put to a trial were his actions were found to be incompatible with the high-ranking status of a doctor, even though he was the unsalaried chief leprologist of Norway until his death. The biography of A. Neisser, who became the culprit of this high-profile scientific scandal, was simultaneously studied. It is shown that a series of A. Neisser's experimental studies on another threatening disease – syphilis, by inoculation also led to a scandal, ironically, similar to that one around the name of Hansen. However, neither his reputation, nor his medical license, or his further scientific career suffered a significan impact, although it has become a precedent for obtaining informed consent from persons taking part in clinical trials. The findings revealed that, despite the desire to serve science and humanity, compliance with the rules of bioethics, as well as human morality, should remain an integral component in the work of any medical scientist.

Keywords: leprosy, Gerhard Hansen, Albert Neisser, Mycobacterium leprae, problems of bioethics.

РЕЗЮМЕ

ГЕРХАРД ХАНСЕН VS. АЛЬБЕРТ НЕЙССЕР: ПРИОРИТЕТ ИЗОБРЕТЕНИЯ MYCOBACTERIUM LEPRAE И ПРОБЛЕМЫ БИОЭТИКИ

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Статья имеет междисциплинарный характер и охватывает широкий круг вопросов истории медицины, морали и биоэтики. Представлены биографии норвежского врача-микробиолога Г. Хансена и немецкого врача, биолога, сифилидолога А. Нейссера. Показано, что любой учёный, даже самый выдающийся, остается человеком с его уникальным характером, личной жизнью и дружескими связями, авторитетом в научном сообществе и фатальными ошибками, желанием достичь славы и признания. Основное внимание акцентировано на научных достижениях этих исследователей инфекционных болезней и лепры, в частности. Описан конфликт, связанный с приоритетом открытия возбудителя лепры. Сравнено, какие последствия для Г. Хансена и А. Нейссера имел международный научный скандал относительно приоритета открытия Mycobacterium leprae, в который было вовлечено практически всё тогдашнее научное европейское сообщество. Показано, что большинство ученых однозначно встало на сторону Г. Хансена, который был не только автором революционной на то время гипотезы о контагиозно-бактериальной природе лепры, но и первооткрывателем возбудителя этой болезни, о чем свидетельствует синонимичное название Mycobacterium leprae – bacillus Hansen. Несмотря на это, для выдающегося ученого последствия неэтичного эксперимента с умышленным дополнительным инфицированием пациентки стали довольно трагическими, поскольку он потерял лицензию на медицинскую практику, пережил суд, по решению которого действия Г. Хансена были признаны несовместимыми с высоким званием врача, хотя он до конца жизни занимал должность внештатного главного лепролога Норвегии. Параллельно исследована биография А. Нейссера, который стал виновником этого громкого научного скандала. Показано, что серия экспериментальных исследований другой опасной болезни – сифилиса, – путем инокуляций, проведенных А. Нейссером, также привела к скандалу, который, по иронии судьбы, походил на тот, который в свое время разразился вокруг имени Г. Хансена. Впрочем, ни на репутацию, ни на медицинскую лицензию, ни на дальнейшую научную карьеру А. Нейссера этот досадный случай существенно не повлиял, хотя стал прецедентом для получения информированного согласия лиц, принимающих участие в клинических испытаниях. В выводах отмечается, что, несмотря на желание служить науке и человечеству, соблюдение правил биоэтики, а также человеческой морали должны оставаться неотъемлемой составляющей деятельности любого ученого-медика.

რეზიუმე

გერხარდ ჰანსენი *VS.* ალბერტ ნეისერი: MYCOBACTERIUM LEPRAE–ს გამოგონების პრიორიტეტი და ბიოეთიკის პრობლემები

[1]ე.ბელიაევა, [2]ე.უვარკინა, [1]ი.ლისანეცი, [3]გ.მოროხოვეცი, [1]ე.გონჩაროვა, [1]მ.მელაშჩენკო

[1]უკრაინის სამედიცინო სტომატოლოგიურ აცადემია, უცხოური ენების კათედრა ლათინური ენით და სამედიცინო ტერმინოლოგიით, პოლტავა; 2უკრაინის ეროვნული ტექნიკურ უნივერსიტეტი "კიევის ი.სიკორსკის სახელობის პოლიტექნიკური ინსტიტუტი", სპეციალური კათედრა №4, კიევი; [3]უკრაინის სამედიცინო სტომატოლოგიური აკადემია, სამეცნიერო განყოფილება, პოლტავა, უკრაინა

სტატია არის ინტერდისციპლინური ტიპის და მოიცავს მედიცინის ისტორის, მორალისა და ბიოეთიკის საკითხების ფართო წრეს. წარმოდგენილია ნორვეგიელი ექიმი-მიკრობიოლოგის გ. ჰანსენისა და გერმანელი ექიმის, ბიოლოგისა და სიფილიდოლოგის ა.ნეისერის ბიოგრაფიები. ნაჩვენებია, რომ ნებისმიერი მეცნიერი, ყველაზე გამორჩეულიც კი, რჩება ადამიანად თავისი უნიკალური ხასიათით, პირადი ცხოვრებით და მეგობრული კავშირებით, ავტორიტეტით სამეცნიერო თანამეგობრობაში და ფატალური შეცდომებით, დიდების და აღიარების მიღწევის სურვილით. ძირითადი ყურადღება აქცენტირებულია ამ

მკვლევარების სამეცნიერო მიღწევებზე ინფექციურ სნეულებებში, სახელდობრ – კეთრის მიმართულებით. აღწერილია კეთრის გამომწვევის აღმოჩენის პრიორიტეტთან დაკავშირებული კონფლიქტი. შედარებულია, რა შედეგები ჰქონდა გ. ჰანსენისა და ა. ნეისერისათვის Mycobacterium leprae-ს აღმოჩენის პრიორიტეტთან დაკავშირებულ საერთაშორისო სკანდალს, რომელშიც ჩართული იყო მაშინდელი ევროპის პრაქტიკულად მთელი თანამეგობრობა. ნაჩვენებია, რომ მეცნიერთა უმეტესობამ ერთმნიშვნელოვნად მხარი დაუჭირა გ. ჰანსენს, რომელიც იყო არა მარტო ავტორი იმ დროისთვის რევოლუციური ჰიპოთეზისა კეთრის კონტაგიოზურ-ბაქტერიული ბუნების შესახებ, არამედ ამ დაავადების გამომწვევის აღმომჩენიც, რასაც მოწმობს სინონიმური დასახელება - Mycobacterium leprae – bacillus Hansen. მიუხედავად ამისა, გამოჩენილი მეცნიერისათვის არაეთიკური ექსპერიმენტის შედეგები პაციენტის ქალის შეგნებული დამატებითი ინფიცირებით საკმაოდ ტრაგიკული აღმოჩნდა: მან დაკარგა ლიცენზია სამედიცინო პრაქტიკაზე, გადაიტანა სასამართლო, რომლის გადაწყვეტილებითაც გ. ჰანსენის მოქმედება ჩაითვალა შეუთავსებლად ექიმის მაღალ წოდებასთან, თუმცა, მას სიცოცხლის ბოლომდე ეკავა ნორვეგიის მთავარი შტატგარეშე ლეპროლოგის თანამდებობა. პარალელურად შესწავლილია ა.ნეისერის ბიოგრაფია, რომელიც ამ ხმაურიანი სკანდალის მიზეზი გახდა. ნაჩვენებია, რომ სხვა საშიში დაავადების – სიფილისის ექსპერიმენტული კვლევის სერიამ, ჩატარებულმა ა.ნეისერის მიერ, ასევე გამოიწვია სკანდალი, რომელიც, ბედის ირონიით, წააგავდა იმას, რომელიც თავის დროზე დატრიალდა გ. ჰანსენის სახელის ირგვლივ. მაგრამ ამ სამწუხარო შემთხვევას ა. ნეისერის არც რეპუტაციაზე, არც სამედიცინო ლიცენზიაზე და არც შემდგომ სამეცნიერო კარიერაზე მნიშვნელოვანი გავლენა არ მოუხდენია, თუმცა, გახდა კლინიკურ კვლევაში მონაწილე პირებისაგან ინფორმირებული თანხმობის მიღების პრეცედენტი. დასკვნით ნაწილში აღნიშნულია, რომ, მეცნიერებისა და კაცობრიობისათვის მსახურების სურვილის მიუხედავად, ბიოეთიკის წესების, ასევე, ადამიანური მორალის დაცვა უნდა წარმოადგენდეს ნებისმიერი მეცნიერი-მედიკოსის საქმიანობის განუყოფელ ნაწილს.

KNOWLEDGE, ATTITUDES AND PERCEPTION AMONG PATIENTS TOWARDS CROSS-INFECTION CONTROL MEASURES IN DENTAL CLINICS IN GEORGIA BEFORE THE COVID-19 PANDEMIC

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Prevention of cross-infection in the dental clinic is a crucial aspect of community protection from infection and dental health care workers should adopt a certain basic infection control routines while practicing [6]. Both dental patients and dental health care professionals are at risk of infections caused by various microorganisms and viruses [8]. Furthermore, nowadays we live in an era of eco-epidemiology [5,4]. Emerging agents in particular HCV, HBV and AIDS/HIV, TB and infectious respiratory diseases having different etiologies and others can be also transmitted during dental practice [9]. More recently, the world has been affected by the coronavirus outbreak (caused by severe acute respiratory syndrome corona virus 2-SARS-CoV-2), which turned into COVID-19 pandemic and embraced the whole world. Health organizations recommended strict preventive strategies for elimination of disease. Despite the considerable emphasis placed on standardized infection control procedures, it appears that few dentists have adhered to these procedures in their clinical practice [10]. Even though, there are many studies carried out with the intention to assess dentist's knowledge towards barrier technique, a very few studies have reported dental patient's awareness about infection control [7]. Importance of patients' knowledge was acknowledged by Centers for Disease Control and Prevention (CDC), which developed several online educational materials to educate the community. It has been demonstrated that adequate patient education can substantially reduce cross infection [1]. Identifying KAP of patients towards infection control methods in dentistry is an important issue. Many studies indicate that compliance of dentists with infection control guidelines was not satisfactory. One of the factors that can bring changes in the compliance is patient expectation. This expectation in turn can be influenced by the media, cultural mores, as well as the patients' level of education. Knowing patient perception of infection control methods will affect dental practice. Heightened awareness among patients will hopefully help them to request and remind members of the dental team to take all necessary steps to prevent cross-infection to protect both their patients and themselves [3].

The objective of the study was to determine the level of knowledge, attitude and perception (KAP) of Georgian patients towards cross-infections and infection control measures in dental clinics. Special attention was paid to issues related to the level of awareness of patients about infections that are quite widespread in the country, in particular HCV, HBV and AIDS/HIV, TB and infectious respiratory diseases having different etiologies

Material and methods. After being approved by the Ethics Committee of the School of Health Sciences of the University of Georgia, this cross-sectional design study was conducted during 2019 among individuals from all 10 regions of Georgia and Tbilisi (the capital city). A non-probability convenience sample method was used. 570 random individuals voluntarily included in the confidenti l study were asked to answer to self-administrated, close-ended questionnaire to assess their knowledge, attitudes, perception (KAP), perception and behaviors toward cross infection control measures in dental clinics. A questionnaire contained 22 questions and consisted of three parts. First part included socio-demographic characteristics (age, gender, level of education, occupation, etc.) and respondent's visits to the dental clinics; the second part included items to assess the

awareness and knowledge about the infection spread and control methods in the dental settings, necessity to use personal protective equipment that dentists should wear such as gloves, gown, mask, goggles, etc. The third part included questions to assess the perceived attitudes and self-reported practices of patients toward infection control measures. Statistical analysis was performed using Statistical Package for Social Sciences (IBM SPSS Statistics, for Windows, Version 23.0. Armonk, NY). Data was presented using descriptive statistics, the Chi-square tests were performed to assess correlations. A statistical significance was considered at P-value <0.05.

Results and discussion. Among 570 participants 71.4% (n 407) were females and 28.6% (n 163) were males. The mean age was 27.83 years. Students made up 43.7 %. 43% of participants were employed. 50.7% of respondents were from Tbilisi, 49.3% were from regions of Georgia. Table 1 shows the demographic characteristics of study participants and respondents distribution according to their visits to the dental clinics.

Second part of the study included patients' knowledge about transmissible infectious diseases in the dental clinic, transmission routes, necessity to use cross-infection barriers and participant's perception of the protective function of cross-infection barriers. In the process of interviewing the respondents, special attention was paid to assessing their knowledge of infections, the prevalence of which is quite high in Georgia. We mean such infectious diseases as HCV, HBV and AIDS/HIV, TB and infectious respiratory diseases having different etiologies. 72.6%, 63.2%, and 62.5% of respondents agreed that they can catch HCV, HBV and AIDS/HIV respectively during dental treatment, while 50.5% and 55.8% mentioned about TB and infectious respiratory diseases respectively (Fig. 1). The present study on the patients' perception of infection transmission in the dental offic was carried out in relation to socio-economic groups assessed according to education level of the participants so as to compare the relative status of awareness at each level. There was a statistically significant relationship between the level of education and knowledge about infectious disease in the dental clinic (Table 2.) P-value=0.005, 0.002, 0.003, and 0.023 respectively for HIV/AIDS, HBV, HCV and infectious respiratory diseases, while the results of Chi-square tests did not show a significant

Table 1. Socio-demographic characteristics of the sample, visits to the dental clinics.

Variables		**No**	**%**
Gender	Males	163	28.6
	Females	407	71.4
Age	<20	220	38.6
	20-30	196	34.4
	31-40	53	9.3
	41-50	49	8.6
	51-60	31	5.4
	>60	21	3.7
Level of education	High school	85	14.9
	Collage	22	3.9
	Bachelor	291	51.1
	Postgraduate	172	30.2
Occupation	Employed	245	43.0
	Unemployed	47	8.2
	Student	249	43.7
	Pupil	23	4.0
	Retiree	6	1.1
Residence	Tbilisi	289	50.7
	Regions (10)	281	49.3
Marital status:	Single	393	68.9
	Married	168	29.5
	Widowed	3	0.5
	Divorced	6	1.1
Last visit to dental clinic	This year	248	43.5
	Last year	158	27.7
	2-3 years ago	164	28.8

relationship between the level of education and knowledge about TB. A statistically significant relationship between gender and knowledge about transmissible infectious disease was found only for HBV and HCV with P-value=0.032 and 0.005 respectively. It is apparent from Table 2 that females obtained a higher percentage of knowledge about infection transmission compared to males. There was a statistically significant relationship between the occupation and knowledge about HIV/AIDS, HBV, HCV with P-value=0.004, 0.023, and 0.000 respectively. No statistically significant relationship was demonstrated between occupation and infection knowledge for TB and infectious respiratory diseases.

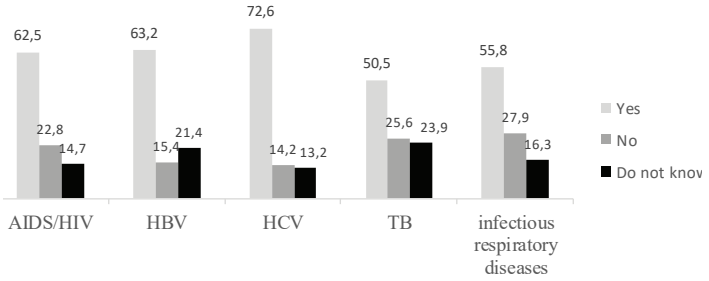

Fig.1. Distribution of patients' knowledge of transmitted infectious disease in the dental clinic

Table 2. Distribution of patients' knowledge of transmitted infectious disease in the dental clinic according to gender, education and occupation

	Gender		**Education**				**Occupation**				
	Male	Female	high school	collage	bachelor	post-graduate	emplo-yed	unem-ployed	retired	student	pupil
	HIV/AIDS (%)										
Yes	55,2	65,4	44,7	72,7	67,7	61	71,8	59,6	0,5	55,8	43,5
No	26,4	21,4	32,9	9,1	21,3	22,1	15,1	29,8	16,7	27,7	39,1
Do not know	18,4	13,3	22,4	18,2	11	16,9	13,1	10,6	33,3	16,5	17,4
χ2 (P value)	***5.279 (0.071)***		***18.774 (0.005)***				***22.562 (0.004)***				
	Hepatitis B (%)										
Yes	54	66,8	52,9	59,1	69,1	58,7	73,1	55,3	66,7	55,8	52,2
No	17,8	14,3	21,2	18,2	14,4	13,4	10,6	21,3	16,6	19,3	17,4
Do not know	27,6	18,7	25,9	182	16,2	27,9	16,3	23,4	16,7	24,9	30,4
χ2 (P value)	***8.820 (0.032)***		***26.260 (0.002)***				***23.539 (0.023)***				
	Hepatitis C (%)										
Yes	65,6	75,4	58,8	68,2	79,7	68,1	82,4	72,3	50	64,7	60,9
No	14,1	14,3	22,4	13,6	11,7	14,5	7,8	14,9	0	20,5	17,4
Do not know	20,2	10,3	18,8	18,2	8,6	17,4	9,8	12,8	50	14,9	21,7
χ2 (P value)	***10.251 (0.006)***		***19.608 (0.003)***				***31.535 (0.000)***				
	TB (%)										
Yes	44,8	52,8	40	59,1	55,6	50,5	57,1	51,1	33,4	44,6	47,8
No	26,4	25,3	31,8	22,7	23,4	25,6	21,6	23,4	33,3	29,7	26,1
Do not know	28,8	21,9	28,2	18,2	21	23,9	21,3	25,5	33,3	25,7	26,1
χ2 (P value)	***3.909 (0.142)***		***9.282 (0.152)***				***9.035 (0.339)***				
	Infectious respiratory diseases (%)										
Yes	51,5	57,5	41,2	54,5	58,1	55,8	59,2	53,2	33,3	54,6	43,5
No	28,2	27,8	41,2	22,8	28,2	27,9	25,3	34	16,7	28,9	34,8
Do not know	20,2	14,7	17,6	22,7	13,7	16,3	15,5	12,8	50	16,5	21,7
χ2 (P value)	***2.910 (0.233)***		***14.712 (0.023)***				***8.823 (0.357)***				

The study describes patients 'knowledge of infection transmission by saliva, blood, non-sterile instruments and routes of transmission. 94% of patients agreed with infection transmission by nonsterile instruments, while only 68.4% and 78.9% agreed with transmission by saliva and blood respectively. 68.4%, 70%, and 77.5% of participants agreed about infection transmission available routes from dentist to patient, from patient to dentist and from patient to patient respectively. Majority of participants (97.9%) had positive attitudes towards infection control measures required during dental practice and agreed that dentists should wear gloves while treating their patients. Similarly, 95.6% and 94% agreed that dentists need to wear face mask and uniform respectively. Only 59.6% of participants agreed about necessity of goggles usage (Fig. 2). 98.2% confirmed that dentists should change gloves for every patient.

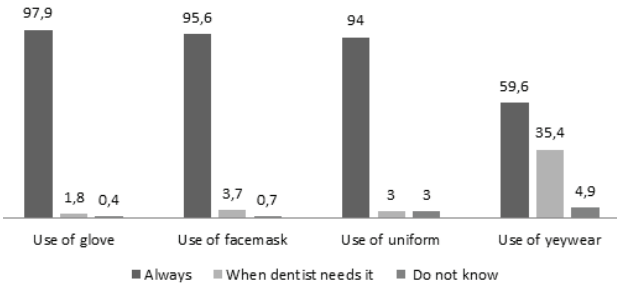

Fig.2. Patients' knowledge of barrier usage in dentistry

Nearly 65.3% and 71.6% of respondents felt that gloves and face masks protect both dentist and patient, respectively. However, 58.4% of respondents believed that wearing of goggles protects dentist only (Fig. 3).

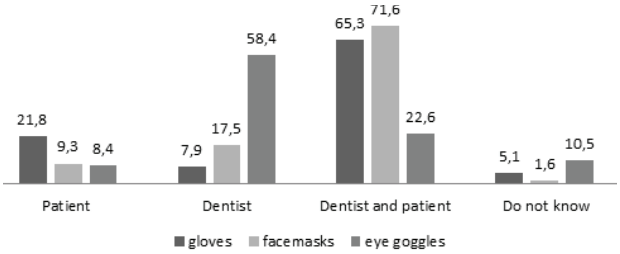

Fig.3. Participant's perception of the protective function of cross-infection barriers

The third part of the study included the questions to assess the perceived attitudes and practices of patients toward infection control measures and is demonstrated patients' particular observation regarding usage of cross-infection barriers by dentists during dental treatment.

94%, 73%, 67.4% and 49.5% of respondents agreed that their dentist always used uniform, gloves, face masks and goggles respectively. 74.6% of participants could observe, how dentist washed hands (Fig. 4).

Patients' attitude and behavior toward poor infection control measures demonstrated that 5.4% complained about poor infection control measures and refused the treatment, 4% - complained, however continued the treatment, 10.5% continued the treatment without complaint, 12.5% refused the treatment without complaint. 67.5% of patients mentioned that treatment complied with rules of infectious safety. 80% of participants are concerned about the risk to be infected during the dental treatment. Moreover, 30.4% have ever avoided dental care due to the risk of getting infected. 62.5% of participants responded that they would not receive treatment in dental clinic where HIV and HBV/HCV patients are being treated. 51.8% of respondents considered that they are protected by the medical staff against infection transmission. 71.4% of patients are satisfied with the quality of dental services (Fig.5).

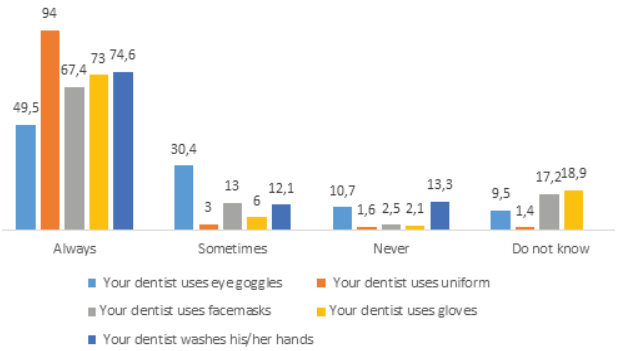

Fig.4. Patients' observation regarding usage of cross-infection barriers by dentist

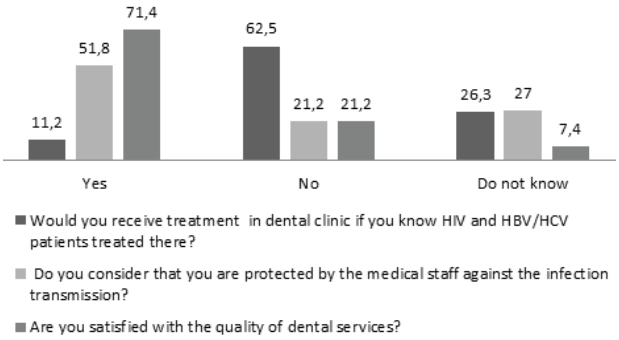

Fig.5. Patients' willingness to receive treatment in the clinic in which infected patients are being treated; Patients' perception regarding protection from cross-infection during treatment; Patients' satisfaction with dental services

To the best of our knowledge, this is the first study done in Georgia for assessing the KAP of dental patients regarding cross-infection and infection control in dental clinics. Following infection control guidelines and use of proper precautions are vital for preventing transmission of bloodborne infections and other dentally acquired cross- infections [2]. In this study about one-third of the participants demonstrated poor knowledge about bloodborne diseases that may be transmitted in dental clinic and nearly half of them showed poor knowledge about transmission of TB and infectious respiratory diseases. Level of knowledge was affected by several socio-demographic characteristics. Nearly one-third of respondents had inadequate understanding of possible routes of infection transmission. Most of participants had positive attitudes towards using of barrier methods by dentist except goggles (59.6%) to prevent spread of infection during dental practice, indicating a high degree of awareness of such matters, while nearly one-third of respondents demonstrated poor knowledge about protective function of cross-infection barriers. Our findings demonstrate the patients' concern and interest towards infection control in the dental office Majority of patients are concerned by the risk to get infected during the dental treatment. Moreover, about one-third of them has ever avoided dental care due to the risk of getting infected. Regarding self-reported practices, about 62.5% of respondents would

not attend a clinic were HIV/AIDS and HBV/HCV patients are being treated. On the other hand, it was reported that nearly half of patients expressed their confidence in the professionalism and responsibility of the medical team regarding infection transmission protection. Infection control practices are crucial and important elements in clinical dentistry as there is an enormous increase in the prevalence of infectious diseases among dental patients, especially nowadays, as we live in an era of eco-epidemiology with global emergence and re-emergence of many communicable diseases. Results of the study highlight importance of the evaluation of patients' perception towards infectious control in dentistry as a method to motivate medical staff to promote safety and increase the quality of dental treatment. In addition, our data emphasize importance of patient education and their involvement in their own safety.

Infection prevention in dentistry is an important topic that has gained more interest in recent years and guidelines for the prevention of cross-transmission are common practice in many countries. However, little is known about the real risks of cross-transmission, specifically in the dental healthcare setting. A number of cases are probably not acknowledged by patients and healthcare workers in dentistry clinics of Georgia. For the above reasons, the real risks of cross-transmission are likely to be higher.

This paper evaluated dental patients needed to be equipped with better knowledge about cross-infection control through more extensive educational programs, increasing public awareness on this issue and the information to determine the risk of cross-transmission of viruses and bacteria that are of particular relevance in the dental practice environment.

Data of this study will assist in providing baseline information while planning effective and efficien public awareness measures on infection control measures in dentistry in Georgia.

There is therefore a need for prospective longitudinal research in this area, to determine the real risks of cross-infection in dentistry. This will assist the adoption of effective hygiene procedures in dental practice.

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SUMMARY

KNOWLEDGE, ATTITUDES AND PERCEPTION AMONG PATIENTS TOWARDS CROSS-INFECTION CONTROL MEASURES IN DENTAL CLINICS IN GEORGIA BEFORE THE COVID-19 PANDEMIC

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Problem of cross-infection and infection in dental practice has become a matter of public concern. Changing public expectations for cross-infection control could improve safety precautions of dental care. Goal of the study was to determine the level of Knowledge, Attitude and Perception (KAP) of Georgian patients attending dental clinics regarding cross-infections and infection control measures in dentistry. A cross-sectional study was conducted among 570 participants from all 10 regions of Georgia and Tbilisi (the capital city) during 2019. A standardized, confidential, self-administered, close-ended questionnaire was used to assess respondents' knowledge, attitudes, self-reported practices, perception and behaviors toward cross-infection control measures in dental clinics. 71.4% (n 407) of participants were females and 28.6% (n 163) were males. 72.6%, 63.2%, and 62.5% of respondents agreed that they can catch during dental treatment HCV, HBV and AIDS/HIV respectively, while 50.5% and 55.8% mentioned about TB and respiratory infectious (RI) diseases respectively. 80% of participants are concerned about the risk to be infected during the dental treatment. 62.5% of participants responded that they would not receive treatment in dental clinic where HIV and HBV/HCV patients are being treated. Overall, the study suggests that participants' knowledge, attitude and perception regarding cross-infection control in dentistry need some improvements. This study will assist in planning more effective interventions to enhance public awareness about infection control in dentistry in Georgia.

Keywords: cross-infection control, Knowledge, Attitude, Perception - KAP, dental patients, perception, behaviors, dental care, IC- Infection Control, Respiratory Infectious (RI).

РЕЗЮМЕ

ЗНАНИЯ, ОТНОШЕНИЕ И ВОСПРИЯТИЕ СТОМАТОЛОГИЧЕСКИХ ПАЦИЕНТОВ К МЕРАМ ПЕРЕКРЕСТНОГО ИНФЕКЦИОННОГО КОНТРОЛЯ В СТОМАТОЛОГИЧЕСКИХ КЛИНИКАХ В ГРУЗИИ ДО ПАНДЕМИИ COVID-19

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Проблема перекрестной инфекции в стоматологической практике стала предметом общественного беспокойства. Изменение общественных ожиданий относительно перекрестного инфекционного контроля могут улучшить меры предосторожности стоматологических услуг. Целью исследования было определение уровня знаний, отношения и практики (KAP) грузинских пациентов, посещающих стоматологические клиники, в отношении перекрестных инфекций и мер инфекционного контроля в стоматологии. В течение 2019 года было проведено перекрестное исследование среди 570 участников из всех 10 регионов Грузии и Тбилиси. Стандартизированная, конфиденциальная, закрытая анкета для самостоятельного применения использовалась для оценки знаний- отношения-практики (KAP) респондентов в отношении контроля перекрестной инфекций в стоматологических клиниках. Анализ данных включал таблицы распределения частот. 71,4% (n 407) участников были женщины, 28,6% (n163) были мужчины. 72,6%, 63,2% и 62,5% 20% респондентов согласились с тем, что во время лечения они могут заразиться гепатитом С, гепатитом В и ВИЧ /СПИД соответственно, в то время как 50,5% и 55,8% упомянули о туберкулезе и инфекционных заболеваниях дыхательных путей соответственно. 80% участников обеспокоены риском заражения во время лечения зубов. 62,5% участников ответили, что не посетят стоматологические клиники, где лечатся пациенты с ВИЧ и гепатитом. В целом, исследование показывает, что знания, отношение и практика участников в отношении перекрестного инфекционного контроля в стоматологии нуждаются в некоторых улучшениях. Это исследование послужит планированию более эффективных мер для повышения осведомленности общества об инфекционном контроле в стоматологии в Грузии.

რეზიუმე

პაციენტების ცოდნა,დამოკიდებულება და აღქმა სტომატოლოგიური კლინიკების ჯვარედინი ინფექციის კონტროლის ღონისძიებების მიმართ Covid-19 პანდემიამდე საქართველოში

თ. ჩიტალაძე, ნ. ყაზახაშვილი

საქართველოს უნივერსიტეტი, ჯანმრთელობის მეცნიერებების სკოლა, თბილისი, საქართველო

სტომატოლოგიური მომსახურების დროს განვითარებული ჯვარედინი ინფექციები საზოგადოებრივი ჯანმრთელობის პრობლემად გადაიქცა. კლინიკაში ინფექციების კონტროლის მიმართ პაციენტთა გაზრდილ მოლოდინებს შეუძლია სტომატოლოგიური სერვისების უსაფრთხოების გაუმჯობესება. კვლევის მიზანს წარმოადგენდა საქართველოს პაციენტთა ცოდნა-დამოკიდებულება-პრაქტიკის შესწავლა-შეფასება სტომატოლოგიურ კლინიკებში ინფექციური კონტროლის ზომების მიმართ. ჯვარედინ-სექციურ კვლევაში მონაწილეობა მიიღო საქართველოს ათივე რეგიონისა და თბილისის 570-მა რესპოდენტმა 2019 წლის განმავლობაში. სტომატოლოგიური კლინიკების ჯვარედინ-ინფექციური კონტროლის ზომების შესახებ მონაწილეთა ცოდნა-დამოკიდებულება-აღქმის (KAP) შესაფასებლად გამოყენებულ იქნა თვითადმინისტრირებადი კითხვარი, მონაწილეობა იყო ნებაყოფლობითი და ანონიმური. მონაცემთა ანალიზი მოიცავდა სიხშირის განაწილების ცხრილებს. კვლევაში მონაწილეობა მიიღო 71.4% (n=407) ქალმა და 28.6% (n=163) მამაკაცმა. გამოკითხულთა 72.6%, 63.2% და 62.5% ეთანხმება, რომ სტომატოლოგიური მკურნალობისას შესაძლოა HCV, HBV და აივ/შიდსის გადადება შესაბამისად; მხოლოდ 50.5% და 55.8% აღნიშნავს ტუბერკულოზისა და ინფექციური რესპირატორული დაავადებების გადადების შესაძლებლობას. მონაწილეთა 80%-ს აღელვებს სტომატოლოგიური მკურნალობის დროს ინფიცირების რისკი. რესპოდენტთა 62.5%-მა უპასუხა, რომ ისინი არ იმკურნალებდნენ იმ სტომატოლოგიურ კლინიკაში, სადაც შიდსითა და ჰეპატიტებით ინფიცირებულ პაციენტებსაც მკურნალობენ. საერთო ჯამში, კვლევა აჩვენებს, რომ მონაწილეთა ცოდნას, დამოკიდებულებას და პრაქტიკას სტომატოლოგიური კლინიკების ინფექციების კონტროლის მხრივ გარკვეული გაუმჯობესება სჭირდება. ეს კვლევა ხელს შეუწყობს საქართველოში სტომატოლოგიის დარგში ინფექციის კონტროლის შესახებ საზოგადოების ცნობიერების ამაღლებას.

ЭВТАНАЗИЯ КАК СПОСОБ РЕАЛИЗАЦИИ ПРАВА ЧЕЛОВЕКА НА ДОСТОЙНУЮ СМЕРТЬ

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Проблема лишения человека жизни всегда была противоречивой, что делает невозможным полное осознание и нормативное ее закрепление. Несмотря на возможности медицины продлевать жизнь человека различными поддерживающими мерами даже при смертельных болезнях, достойное социальное существование человека иногда становится невозможным. Поэтому вопрос облегчения человеческих страданий, гуманного отношения к человеку и его жизни, а также реализация права человека на смерть с помощью процедуры эвтаназии приобретает актуальность во всем мире.

Окончательной позиции по поводу легализации эвтаназии еще не сформировано, поэтому она всегда будет вопросом из категории «быть или не быть». Каждое общество, страна и человек всегда будут стоять перед выбором, который должен быть гарантированно закреплен на государственном уровне. Исходя из вышеизложенного, правовая оценка эвтаназии, ее квалификация с точки зрения национального, особенно уголовного законодательства является весьма актуальной.

Отсутствие в законодательстве Украины правовых актов, регламентирующих процедуру эвтаназии и механизмы ее регулирования, не предоставляют возможность осуществлять ее правовую оценку, искажают объективное понимание феномена эвтаназии и необходимости ее легализации. Запрещая эвтаназию, государство лишает человека права распоряжаться своей жизнью, что является антигуманным и безнравственным. Признание права человека на достойную смерть закрепленное законодательством и его нормативное регулирование позволит признать ценность человеческой жизни, ее социальную значимость, приведет к абсолютно новому пониманию человека, как уникального существа, уважению его взглядов, убеждений, желаний и станет основанием для проведения процедуры эвтаназии.

Целью исследования является осуществление комплексного анализа феномена эвтаназии в контексте реализации права человека на смерть для ее легализации в Украине; основной задачей – обобщить опыт стран ЕС по вопросу легализации и проведения эвтаназии и с учетом результатов, определить основные пути совершенствования законодательства Украины в этом вопросе.

Материал и методы. Для достижения поставленной цели использованы общенаучные и специальные методы познания: диалектический метод – для поиска адекватных подходов к решению теоретических и правовых проблем, возникающих при правовом регулировании процедуры эвтаназии; системный метод – для исследования права человека на смерть как одной из составляющей права на жизнь; функциональный метод – для установления субъектов процедуры эвтаназии; аксиологический подход – при определении содержания эвтаназии как способа реализации права человека на достойную смерть; сравнительно-правовой метод применялся для анализа правовых актов по вопросам организации и проведения эвтаназии и формулирования предложений по усовершенствованию украинского законодательства; формально-логический метод – для формулирования авторского понятия эвтаназии и определения процедуры ее легализации в Украине с учетом комплексного анализа европейского законодательства.

Результаты и обсуждение. *Эвтаназия: избавление человека от страданий или убийство?*

Гуманизация законодательства и формирование прав человека четвертого поколения ставит перед мировым сообществом вопрос, что является целью любого правового и демократического государства – жизнь человека и ее защита или обеспечение достойного существования. Человек и его жизнь, как общепризнанная ценность, находят свое закрепление в международных нормативно-правовых актах, среди которых Европейская конвенция по правам человека (р.2), Всеобщая декларация прав человека (р.3), Международный пакт о гражданских и политических правах (р.6), Конвенция о правах ребенка (р.6), Конвенция о защите прав человека и основных свобод (р.2). Все вышеперечисленные акты гарантируют неприкосновенность человеческой жизни, однако не позволяют человеку распоряжаться ею несмотря на то, что жизнь человека не является собственностью государства и только сам человек имеет право самостоятельно решать, когда закончится этот процесс. Речь идет о нормативно закрепленной возможности человека уйти из жизни в исключительных случаях при наличии имеющихся медицинских показателей: тяжелая неизлечимая болезнь, переживание постоянных физических мук и страданий, вызванных болезнью, невозможность полноценного достойного социального существования и избавления от мучений. Право на смерть является неотъемлемой частью и средством полной реализации права на жизнь [4, с. 178]. Следовательно, значимым фактором является гуманное отношение к человеку и закрепление в законодательстве его права на смерть, которое должно быть обдуманным и сознательным волеизъявлением, принятым с учетом и критическим пониманием всех последствий такого действия. Именно эвтаназия способна обеспечить реализацию принципа гуманизма – одного из основополагающих принципов права, поэтому право на эвтаназию – это право не ради всех, а для конкретной группы лиц, которые в силу определенных обстоятельств нуждаются в ней [4].

Само понятие «эвтаназия» является полисемантическим, сочетает в себе медицинский, биологический, религиозный, правовой, морально-этический аспекты, чем и вызвано неоднозначное отношение социума к этому феномену. Анализируя труды специалистов в области медицины Дж. Перейра, Р. Хакстейбла, А. Патила следует отметить, что эвтаназию они определяют как деяние, совершенное врачем с целью намеренно прекратить жизнь неизлечимо больного человека по его просьбе [8,11,12]. Однако существуют еще ряд признаков, которые характеризуют эвтаназию, поэтому поддерживая такую позицию необходимо учитывать, что эвтаназией является деяние медицинского работника, которое направлено на прекращение жизни неизлечимо больного пациента с целью уберечь его от невыносимых страданий, по просьбе самого больного или его законных представите-

лей, в случаях, когда сам пациент не в состоянии озвучить такое желание самостоятельно и, естественно, только при наличии медицинских показаний о том, что его полноценное, достойное социальное существование невозможно.

Вопрос применения эвтаназии по сей день является дискустабельным не только в Украине, но и во всем мире, и останется таковым до формирования в обществе полноценного понимания необходимости признания права человека самостоятельно распоряжаться своей жизнью. Украинское общество неоднозначно относится к процедуре эвтаназии и не всегда принимает желание человека уйти из жизни. Об этом свидетельствует отсутствие данного института в Украине и каких-либо правовых норм, регламентирующих эту процедуру.

Действующее законодательство Украины строго запрещает совершение эвтаназии в любой форме. Нормативное закрепление эвтаназии содержится в ч. 7. ст. 52 Закона Украины «Основы законодательства Украины о здравоохранении», где указано, что «…медицинским работникам запрещается осуществление эвтаназии – преднамеренного ускорения смерти или умерщвление неизлечимо больного с целью прекращения его страданий» [3]. Согласно п. 1 этой же статьи запрещено применение пассивной эвтаназии, «... медицинские работники обязаны оказывать медицинскую помощь в полном объеме пациенту, который находится в неотложном состоянии, а активные меры по поддержанию жизни пациента прекращаются в случае, когда состояние человека определяется как необратимая смерть» [3].

Прямое указание на процедуру эвтаназии в каком-либо нормативно-правовом акте Украины отсутствует. Эвтаназия косвенно упоминается лишь в ч. 4 ст. 281 Гражданского кодекса Украины, где зафиксировано, что «запрещается удовлетворение просьбы физического лица о прекращении его жизни» [6]. Однако, учитывая особенности эвтаназии, среди которых ключевой является совершение деяния специальным субъектом, в частности медицинским работником, не совсем понятно, что имеет в виду законодатель, устанавливая такой запрет.

Уголовный кодекс Украины (далее – УК Украины) не содержит нормы относительно убийства, совершенного по просьбе пациента или по мотивам чувства жалости к нему, а следовательно, данное деяние квалифицируется по ч. 1 ст. 115 УК Украины, то есть как простой состав убийства [2]. Необходимо отметить, что законодатель лишение жизни путем эвтаназии не определяет как смягчающее обстоятельство при назначении наказания, несмотря на то, что в ч. 2. ст. 115 УК Украины отмечено: «при назначении наказания суд может признать смягчающими и другие обстоятельства, не указанные в ч. 1 ст. 115 УКУ» [2], тем самым допуская вероятность признания лишения жизни путем эвтаназии, как смягчающее обстоятельство.

Анализируя такой подход законодателя к квалификации эвтаназии следует отметить, что он является критически неправильным как с точки зрения права, так и с точки зрения морали. Квалифицируя эвтаназию как простой состав убийства, закон ставит знак равенства между двумя совершенно разными деяниями: лишением жизни путем эвтаназии и умышленным убийством по мотивам мести, ревности, личной неприязни, между осознанным и желанным убийством человека в результате какого-то личного конфликта и лишением жизни человека, который болен смертельной или неизлечимой болезнью, испытывая муки и страдания. Очевидно, что такое соотношение действий сводит на нет все задачи уголовного законодательства и механизмы защиты прав человека в отношении преступлений против его жизни и здоровья. Таким образом, эвтаназия, как уголовно наказуемое деяние, не имеет состава преступления, т.е. не содержит всех необходимых конструктивных признаков для выделения ее в группу преступлений против жизни и здоровья человека.

Отсутствие критически значимых аспектов в субъективной и объективной стороне этого деяния, в частности лишение жизни смертельно больного пациента, не может характеризоваться как посягательство на его жизнь, поскольку не содержит общественно опасных последствий, т.е., поскольку эвтаназия является реализацией права на смерть каждого человека, то и касается она исключительно самой личности и ее интересов, а следовательно, не нарушает общественный порядок, конечно при условии, что она осуществляется по неоднократному сознательному волеизъявлению больного и исключительно как его добровольное желание.

Следует понимать, что прекращая жизнь больного по его требованию, когда имеется подтвержденный факт невыносимых мук от неизлечимой или длительной болезни, которая исключает достойное человеческое существование, а также при неоднократном желании пациента уйти из жизни субъект этого действия не имеет ни умысла, ни мотива преступления. Поэтому в деянии отсутствует субъективная сторона, свидетельствующая об отсутствии состава преступления, то есть не представляется возможным квалифицировать эвтаназию как преступление против жизни и здоровья человека. Так, умысел, имеющий интеллектуальный и волевой признаки, при осуществлении эвтаназии у субъекта такого преступления полностью отсутствует (в частности, речь идет о волевом аспекте и желании достичь конкретного преступного результата, поскольку деяние совершается по решению пациента, а не по воле или желанию того, кто проводит процедуру эвтаназии). Таким образом, проведение эвтаназии не является волевым поведением субъекта данного деяния, а значит не вызывает у него определенных осознанных побуждений к совершению преступления.

Отсутствие судебной практики и правовой регламентации эвтаназии в Украине наводит на мысль о несуществовании указанного вида преступления, приравнивая её к простому убийству и делая невозможным сбор объективных данных об этом деянии.

Анализ законодательства европейских стран по вопросам легализации эвтаназии.

Сегодня ряд европейских стран, таких как Албания, Бельгия, Голландия, Люксембург, Нидерланды, Швейцария (Цюрих), Швеция, Германия на законодательном уровне признали право человека на смерть и не считают эвтаназию уголовно-наказуемым деянием.

Легализировав активную эвтаназию путем принятия «Review Procedures for the Termination of Life on Request and Assisted Suicide and Amendment of the Criminal Code and the Burial and Cremation Act» Нидерланды предоставили разрешение на ее проведение. Право на эвтаназию получили все граждане, достигшие 16 лет (лицам, не достигшим 16-летнего возраста необходимо получить разрешение законных представителей). Целью нидерландского законодательства было облегчение мук и страданий неизлечимо больных, делающие невозможным их дальнейшее достойное существование [15]. Поэтому указанный закон не противоречит ст. 6 Международного пакта о гражданских и политических правах и ст. 2 Европейской Конвенции по правам человека.

Стоит поддержать позицию G. Kimsma, указывающего на различия между вмешательством в процесс жизни человека в конце его завершения, что относится к «нормальной медицинской практике», с тем, что называется «ненормальной» медицинской практикой. Поэтому смерть в результате отказа от лечения с целью уменьшить боль и страдания, включая паллиативную помощь, следует считать нормальной медицинской практикой. Эвтаназию или асистированное самоубийство, без просьбы самого больного является ненормальной медицинской практикой [9].

В Нидерландах эвтаназия признается исключительно медицинской процедурой, так как целью нидерландского законодательства является закрепление в нем исключительно гуманного отношения к больному, что заключается в лишении его жизни по собственному желанию в случае, если он претерпевает нечеловеческие мучения, вызванные смертельной или неизлечимо тяжелой и длительной болезнью [9]. Поэтому эвтаназия не рассматривается как умышленное лишение жизни другого человека и связанные с ней процедуры не содержат состава преступления.

Анализируя законодательство Бельгии по вопросам эвтаназии, в частности закон «The Belgian Act on Euthanasia» of May необходимо отметить, что его базисом является законодательная практика Нидерландов. Однако, в отличие от голландского закона, бельгийское законодательство содержит не только дефиницию этого деяния, определяя эвтаназию как действие, совершаемое третьим лицом, которое сознательно прекращает жизнь другого человека по его собственной просьбе [13], но и содержит разработанный механизм контроля за реализацией права на эвтаназию, возлагая его на специально созданную Федеральную комиссию по контролю и оценке эвтаназии [13].

Определение «эвтаназии», предложенное бельгийским законодателем, включает в себя только часть характерных признаков этого деяния, раскрывая их в дальнейших статьях закона. На абстрактность и несовершенство дефиниции этого понятия указывает отсутствие в нем упоминания специального субъекта, наличие у лица неизлечимой болезни и страданий от нее, а также отсутствие умысла и мотива у субъекта действия, которое осуществляется по просьбе больного человека. Поэтому дополнение дефиниции эвтаназии всеми характерными признаками позволит избежать двойной трактовки понятия при применении норм этого закона. Определенные противоречия в бельгийском обществе вызывают и положения вышеупомянутого закона о разрешении на проведение эвтаназии несовершеннолетним. Однако, при условии полного соблюдения всех правовых норм, следует считать его эффективным и безопасным механизмом реализации права человека на смерть, вводящим институт эвтаназии.

Отдельного внимания заслуживает законодательная практика применения эвтаназии в Швейцарии, согласно которой помощь в совершении самоубийства неизлечимо больным не считается нарушением закона. Так, в соответствии со ст. 115 Уголовного кодекса Швейцарии за причинение смерти другому лицу из корыстных или любых других мотивов законодатель предусматривает уголовную ответственность [16]. Аналогично регулируется такое же деяние из благих намерений, в частности из жалости или сострадания [13]. При соблюдении предусмотренных законодательством условий, помощь в совершении самоубийства больным лицам законодательством не запрещена и не квалифицируется как лишение жизни другого человека. Таким образом, Верховный суд Швейцарии установил, что «... люди должны знать о действиях, которые они могут предпринять, и должным образом следует учитывать их ситуацию. Кроме того, если они будут постоянно уверены, что хотят умереть, и, конечно, не под влиянием другого человека или группы лиц, такое желание должно быть удовлетворено .. » [10], Для реализации указанных норм в Швейцарии созданы специальные организации, которые на платной основе предоставляют услуги по самоубийству как своим гражданам, так и гражданам другой страны путем изготовления специальных препаратов для прекращения жизнедеятельности человека, введение которых в свой организм человек совершает самостоятельно. Швейцарское законодательство предусматривает наличие и функционирование специализированных учреждений, осуществляющих эвтаназию не только для собственных граждан, но и для иностранцев при наличии документально подтвержденного факта тяжести заболевания у конкретного лица.

Анализируя положение бельгийского законодательства, следует отметить, что применение такой модели «легкой смерти» в Украине и в мире недопустимо, поскольку не дает возможности урегулировать эту процедуру и контролировать ее, а также создает предпосылки к пособничеству в самоубийстве со стороны других лиц. Поэтому применять указанный опыт в Украине нецелесообразно. В противном случае это может привести к увеличению процента преступлений связанных с превышения медицинским персоналом своих полномочий. Поддерживая идеи профессора M. Brazier, считаем необходимым закрепить право на осуществление эвтаназии не за доктором, а за специальным лицом с медицинским образованием – лицензированным танатологом [7].

Анализируя европейское законодательство стоит упомянуть Люксембург и закон «The Law on euthanasia and assisted suicide», позволяющий прекращать жизнь больного по его просьбе при условии согласования этого деяния двумя врачами и комиссией экспертов [14], легализовав таким образом эвтаназию и предоставив человеку самостоятельно распоряжаться собственной жизнью.

Ряд европейских стран, (например, Германия) также поддерживают применение эвтаназии, о чем свидетельствует принятое ими законодательство. Касательно Франции, то она изначально поддержала эвтаназию, но через несколько лет отказалась от нее. В Германии Федеральный конституционный суд принял решение, согласно которому право на смерть по собственному желанию признано как личное неотъемлемое право человека. При этом суд указал, что запрет эвтаназии нарушает права тяжелобольных. Однако пока немецким парламентом не принято ни одного законопроекта относительно процедуры осуществления эвтаназии [5].

Таким образом, легализация процедуры эвтаназии и эвтаназийной практики странами ЕС свидетельствует о ее актуальности и необходимости дальнейшего законодательного урегулирования.

Выводы. Эвтаназия, как процедура прекращения жизни человека, совершаемая по осознанному волеизъявлению больного человека, не содержит в себе антигуманных факторов, и поэтому не может приравниваться к убийству, поскольку является исключительным правом человека самостоятельно распоряжаться своей жизнью. Она не является нарушением права на жизнь, закрепленного в Конституции Украины, в которой законодатель гарантирует человеку лишь право на жизнь [1], а не саму жизнь, следовательно, дает свободу распоряжаться своей жизнью. Исходя из вы-

шеизложенного, нельзя судить об эвтаназии в контексте произвольного лишения жизни, поскольку сам пациент дает согласие на такое действие.

На сегодняшний день Европейский Суд по правам человека официально не признает право человека на достойную смерть, а эвтаназию как способ его реализации. Однако все больше стран легализуют «легкую смерть» и создают законодательную базу для ее закрепления. Следует признать, что суть проблемы эвтаназии, как правило, сводится к проблеме выбора, которая включает не только выбор самого пациента «жить или не жить», но и отношение общества к этому феномену.

Очевидно, что вскоре перед Украиной тоже встанет вопрос легализации эвтаназии и закрепления четкого механизма урегулирования этого вопроса. Сам факт легализации эвтаназии должен найти свое отражение в Конституции Украины, гарантировав человеку право на смерть, предусмотрев изменения в медицинском, уголовном и гражданском законодательстве.

Изучив законодательную практику ряда европейских стран в этом вопросе, следует отметить, что их идеи должны быть усовершенствованы и интегрированы в украинскую правовую систему с учетом историко-культурных ценностей и менталитета украинских граждан. Эвтаназийная практика должна приобрести новое содержание и найти свое отражение в отдельном правовом институте. С целью легализации эвтаназии в Украине необходимо: 1) закрепить в Конституции Украины право на смерть, как способ реализации права человека на жизнь; 2) декриминализировать эвтаназию и принять закон «О реализации права на достойную смерть»; 3) создать отдельный институт эвтаназии как области медицины, так и юриспруденции.

Первым и ключевым шагом легализации эвтаназии в Украине является признание и нормативное закрепление права человека на смерть и его реализацию в контексте права на жизнь. Конституция Украины должна гарантировать человеку возможность полноценно распоряжаться собственной жизнью на любом биологическом этапе его существования. Украинское законодательство должно предоставить человеку право выбора относительно возможности достойно уйти из жизни в случае наличия у него тяжелой неизлечимой болезни, не обязывая его жить, переживать муки и страдания и гарантируя полноценный способ реализации права на жизнь, включая распоряжения ею.

После закреплением права на достойную смерть встанет вопрос о способах его реализации, и собственно, на этом этапе станет возможным утверждение и понимание необходимости процедуры эвтаназии в человеческом сознании. Для этого нужно декриминализировать эвтаназию. Введение понятия «эвтаназии» в правоприменительную практику поможет различать убийство человека от действия, направленного на прекращение жизни неизлечимо больного. Поэтому сверхважно четко на законодательном уровне закрепить понятие «эвтаназии» со всеми ее признаками для предотвращения двоякого трактования этого деяния.

Закон Украины «О реализации права на достойную смерть» должен содержать определение и другие понятия эвтаназийной практики, перечень актов, регулирующих данные правоотношения, процедуру и полномочия специального органа, который будет ее регулировать, условия применения и проведения эвтаназии, права и обязанности пациента и медицинского работника, который будет осуществлять эвтаназию, перечень необходимых медицинских документов для проведения эвтаназии, механизм контроля за проведением эвтаназии, ответственность за нарушение законодательства о правах человека на достойную смерть, гарантии участникам процедуры эвтаназии.

Законодательное закрепление эвтаназийных правоотношений позволит создать независимый институт эвтаназии как в юриспруденции, так и в медицине. Украина должна взять за основу такую идею легализации эвтаназии, в которой базисом станет ее осуществление исключительно медицинским работником, с соблюдением всех необходимых медицинских протоколов. Указанная норма не только позволит закрепить объективную и обоснованную возможность больного уйти из жизни, но и не допустит превращения добровольной эвтаназии в принудительную и декриминализует само деяние.

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SUMMARY

EUTHANASIA AS A WAY TO REALIZE THE HUMAN RIGHT TO THE DEATH WITH DIGNITY

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The purpose of the research is to carry out a comprehensive analysis of the phenomenon of euthanasia in the context of realizing the human right to death in order to legalize it in Ukraine. The main objective of the article is to summarize the experience of the EU countries on the issue of legalization and conduction of euthanasia and to determine the main ways of improving the legislation of Ukraine on this matter, taking into account the abovementioned experience. While writing the article, the author has used general scientific and special legal methods. A comprehensive analysis of the legislation of European states has been carried out in order to formulate the author's vision of the concept of euthanasia and the procedure for its legalization in Ukraine.

The main focus of the article is on the fact that euthanasia cannot be qualifi d as murder, since it is the exclusive right of a person to independently control his or her life. The legislation of a number of European countries has been analyzed. On this basis the author has argued on the expediency of introducing the institution of euthanasia in Ukraine. The necessity of consolidating the right to death in the Constitution of Ukraine as a way of realizing the human right to life has been substantiated. It has been proved that the presence of such a legal norm in Ukrainian legislation will prevent voluntary euthanasia from becoming compulsory and will depenalize the act itself. The author has offered to legalize euthanasia and the practice on euthanasia in Ukraine by adopting the Law of Ukraine "On Realizing the Right to the Death with Dignity".

Keywords: euthanasia, right to life, legalization of euthanasia, realization of the right to death, practice on euthanasia.

РЕЗЮМЕ

ЭВТАНАЗИЯ КАК СПОСОБ РЕАЛИЗАЦИИ ПРАВА ЧЕЛОВЕКА НА ДОСТОЙНУЮ СМЕРТЬ

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Целью исследования является осуществление комплексного анализа феномена эвтаназии в контексте реализации права человека на смерть с целью ее легализации в Украине. Основная задача – обобщить опыт стран ЕС в вопросе легализации и проведения эвтаназии и с учетом этого опыта определить основные пути совершенствования законодательства Украины в этом вопросе. Использовались общенаучные и специально-правовые методы, осуществлен комплексный анализ законодательства европейских государств с целью формулирования авторского видения понятия эвтаназии и процедуры ее легализации в Украине.

В статье акцентировано внимание на том, что эвтаназия не может квалифицироваться как убийство, поскольку является исключительным правом человека самостоятельно распоряжаться своей жизнью. Проанализировано законодательство ряда европейских стран, на основе которого аргументирована целесообразность введения института эвтаназии в Украине. Обоснована необходимость закрепления в Конституции Украины права на смерть, как способа реализации права человека на жизнь. Доказано, что наличие такой правовой нормы в украинском законодательстве не допустит превращения добровольной эвтаназии в принудительную и декриминализует само деяние. Предложено легализировать эвтаназию и эвтаназийную практику в Украине путем принятия закона «О реализации права на достойную смерть».

რეზიუმე

ევთანაზია, როგორც ადამიანის ღირსეული სიკვდილის რეალიზაციის გზა

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კვლევის მიზანს წარმოადგენდა ევთანაზიის ფენომენის ყოვლისმომცველი ანალიზი ადამიანის სიკვდილის უფლების რეალიზაციის კონტექსტში უკრაინაში მისი ლეგალიზაციის მიზნით, ხოლო მთავარი ამოცანა

- ევროკავშირის ქვეყნების გამოცდილების შეჯამება ლეგალიზაციისა და ევთანაზიის საკითხში და მისი გათვალისწინებით, ამ საკითხში უკრაინის კანონმდებლობის გაუმჯობესების ძირითადი გზების დასახვა. საკითხის დამუშავებისას გამოყენებულია ზოგადი სამეცნიერო და სპეციალური იურიდიული მეთოდები, გაანალიზებულია ევროპული სახელმწიფოების კანონმდებლობა, შემოთავაზებულია ავტორების ხედვა ევთანაზიის კონცეფციის და უკრაინაში მისი ლეგალიზაციის პროცედურის შესახებ.

სტატიაში ყურადღება გამახვილებულია იმ ფაქტზე, რომ ევთანაზია არ შეიძლება შეფასდეს, როგორც მკვლელობა, რადგან მისი განსაკუთრებული უფლებაა, ადამიანმა დამოუკიდებლად აკონტროლოს თავისი ცხოვრება. გაანალიზებულია ევროპის რიგი ქვეყნების კანონმდებლობა, რის საფუძველზეც დასტურდება უკრაინაში ევთანაზიის ინსტიტუტის შემოღების მიზანშეწონილობა. დასაბუთებულია უკრაინის კონსტიტუციაში სიკვდილის უფლების უზრუნველყოფის აუცილებლობა, როგორც ადამიანის სიცოცხლის უფლების რეალიზაციის გზა. დადასტურებულია, რომ ასეთი სამართლებრივი ნორმის არსებობა უკრაინის კანონმდებლობაში არ დაუშვებს ნებაყოფლობითი ევთანაზიის სავალდებულო გარდაქმნას და თავად ქმედების დეკრიმინალიზაციას. შემოთავაზებულია უკრაინაში ევთანაზიისა და ევთანაზიის პრაქტიკის ლეგალიზება კანონის მიღებით «ღირსეული სიკვდილის უფლების განხორციელების შესახებ».

СОВРЕМЕННОЕ СОСТОЯНИЕ РЕФОРМЫ ЗДРАВООХРАНЕНИЯ В УКРАИНЕ В УСЛОВИЯХ ЕВРОИНТЕГРАЦИИ

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Изменение политической ситуации в Украине привело к реформированию большинства сфер жизнедеятельности как людей, так и государства в целом. Не является в этом плане исключением и система здравоохранения. Использование пережитков советской системы привело к тому, что граждане отказывались пользоваться системой здравоохранения, которая не отвечала их потребностям. Такая не эффективная управленческая системы имела место в финансировании, кадровом обеспечении системы, что, в целом, привело к ухудшению здоровья населения, обострению проблемы не эффективного использования финансовых ресурсов, усилению неравенства в доступе к медицинской помощи. Модернизация первичной и неотложной медицинской помощи, которая была начата, не сопровождалась позитивными изменениями в других сферах системы, поскольку была лишь поверхностными действиями. Поэтому было принято решение перехода на новую модель системы здравоохранения, которая должна сопровождаться тщательным контролем.

Актуальность реформы здравоохранения обусловлена не только необходимостью изменений в этой сфере, но и необходимым условием для процессов европейской интеграции Украины. Как отметил В. Костюк, реализация права человека на качественные медицинские услуги определяет направление государственной политики в Украине по реформированию действующей системы здравоохранения и созданию эффективной национальной модели [4].

Теоретически и практически вопросы, касающиеся механизмов реформирования здравоохранения в Украине являются предметом многих научных исследований. Среди них работы: О. Андрушко, В. Бабченко, О. Боброва, М. Заярского, В. Костюк, Л. Крячкова, В. Лехана, И. Молень и другие. Реформа здравоохранения – одна из самых актуальных проблем сегодня, особенно для Украины, которая находится только на начальном пути реализации изменений в этой сфере.

Цель исследования – выявить наиболее актуальные проблемы медицинской реформы, определить суть медицинской реформы, указать ее возможные плюсы и минусы.

Материалы и методы. Для анализа процесса реализации изменений в сфере здравоохранения и достижения результатов в этом процессе были использованы следующие методы: сравнительно-правовой, статистический, индукционный, анализ, синтез.

Результаты и обсуждение. После распада Советского Союза в 1991 году стало ясно, что семашковская модель здравоохранения, которая была успешной в СССР до 1970-х годов, не соответствовала ни реалиям рыночной экономики, ни устоявшемся типу неэпидемической патологии. Во всех постсоветских странах, включая Украину, начались преобразования в системе здравоохранения, которые касались реорганизации организации, финансирования и оказания медицинских услуг [5]. Трансформационные процессы, происходящие сегодня в Украине в сфере здравоохранения, направлены на его переход от административно-командной модели к прозрачным экономическим и правовым механизмам, где каждый участник этих отношений заинтересован в более эффективном получении или предоставлении медицинских услуг. Существующее разделение экономических отношений в соответствии с действующим Хозяйственным кодексом Украины предусматривает два типа управления: коммерческое и некоммерческое. Некоммерческий менеджмент – очень важная форма совмещения рыночного и товарно-денежного характера медицинских услуг и в то же время учитывающая особенности социальных приоритетов общества.

Поэтому реформирование сферы здравоохранения стало актуальной проблемой, решение которой – не только необходимость времени, но и условие евроинтеграционных процессов в Украине. Следовало придать новый импульс реформе отрасли с помощью новых стратегических подходов, улучшающих качество и доступность помощи и

снижающих финансовые риски для людей. В связи с этим в августе 2014 года Минздрав инициировал разработку «Национальной стратегии реформирования здравоохранения в Украине» [7]. Основными направлениями, предусмотренными этой Стратегией являются: стимулирование правильных реформ, демонстрация лицам, принимающим решения, что здоровье и здравоохранение являются мощным инструментом в политике.

На основе концептуальных положений «Национальной стратегии реформирования здравоохранения Украины» Минздрав инициировал, разработал и принял ряд нормативно-правовых актов, задачей которых было не только «запустить» реформу в целом, но и регулировать ее на соответствующих этапах реализации. Среди них: «Концепция реформы финансирования здравоохранения», Закон Украины «О государственных финансовых гарантиях медицинской помощи», Закон Украины «О внесении изменений в некоторые законодательные акты Украины по совершенствованию законодательства об учреждениях здравоохранения», Постановление Кабинета Министров Украины «Некоторые вопросы по договорам оказания медицинской помощи населению в рамках программы медицинских гарантий», Положение «О Национальной службе здравоохранения Украины» и др.

Например, «Концепция реформы финансирования здравоохранения» предполагает, что реформа направлена на предоставление гражданам Украины доступа к уровню медицинской помощи, достойному европейского государства, путем перевода системы здравоохранения Украины на финансирование на основе модели обязательного государственного медицинского страхования граждан за счет средств государственного бюджета [9]. Как отмечают В. Бабченко и О. Андрушко, реформа предполагает, прежде всего, структурную перестройку, которая включает четкое разграничение начального, среднего и высшего уровней; обеспечение приоритетного развития первичной медико-санитарной помощи с упором на ее профилактическую составляющую; внедрение современных механизмов организации медицинской помощи, таких как свободный выбор врача первичной помощи и система направлений на вторичный и третичный уровни; внедрение эффективной системы управления качеством медицинской помощи с использованием медицинских стандартов и клинических протоколов, основанной на достоверных научных данных [1].

Принимая во внимание основные положения «Национальной стратегии реформирования здравоохранения в Украине», нормативно-правовую базу, принятую для достижения целей и направления процессов реформирования здравоохранения, сегодня мы можем сформулировать основные направления реформы здравоохранения в Украине. Первое направление связано с оказанием медицинских услуг. Следует отметить, что в Украине сложилась ситуация, когда медицинские услуги не оказывались на том уровне, который должен быть в этой сфере. Для решения этой проблемы было решено создать свободный рынок медицинских услуг, который будет представлять не только государственных игроков, но и частный сектор, а медицинские учреждения, в отличие от устоявшейся советской модели, будут иметь полную автономию в плане организационно-правовой формы. Как юридические лица они будут преобразованы из бюджетных учреждений в некоммерческие предприятия. Фактически предусматривается создание конкурентного рынка медицинских услуг.

Основная роль в новой системе здравоохранения отведена первичной медико-санитарной помощи или так называемым семейным врачам. Именно к ним обращаются пациенты с их заболеваниями, и именно семейный врач иметь исключительное право направлять их к специализированным врачам [3]. Следует отметить, что первый этап медицинской реформы, относящийся к первичному звену, по мнению большинства специалистов, прошел достаточно успешно. Семейные врачи получили значительную прибавку к зарплате (иногда в три раза), а пациенты получили качественные услуги. Согласно опросам общественного мнения, почти 70% украинцев, заключивших договор со своим врачом, довольны качеством этих услуг. Следующий шаг – вторичный с постепенным переходом на третичную помощь (специализированную и узко специализированную). Основная идея, пронизывающая все три этапа – «деньги должны идти за пациентом». Следует отметить, что второй этап трансформации финансирования здравоохранения уже начался.

Второе направление – это финансирование системы здравоохранения. Главный принцип, который должен действовать в сфере здравоохранения при оказании медицинских услуг, – это внедрение модели государственного солидарного медицинского страхования. Такая модель должна учитывать современные передовые практики и опыт преобразования систем здравоохранения в мире в целом, и в Центральной и Восточной Европе в частности. Средства, выделяемые из бюджета на финансирование медицины, в соответствии с основным принципом реформы, распределяются через новый, современный механизм стратегических закупок медицинских услуг, который заключается в внедрении принципа «деньги следуют за пациентом».

По состоянию на конец 2020 года с Национальной службой здравоохранения Украины законтрактовано 3095 поставщиков медицинских услуг населению, которым выплачено 51,6 млдр. грн. за предоставление услуг пациентам по Программе медицинских гарантий. Из них: 13,3 млдр. грн. выплачено учреждениям первичного звена; 29,7 млдр. грн. – заведениям, предоставляющих вторичную (специализированную) помощь; 3,7 млдр. грн. – заведениям экстренной медицинской помощи. Также 4,9 млдр. грн. выплачено медицинским учреждениям, оказывающим помощь пациентам больным COVID-19 или с подозрением на него.

С января по сентябрь 2020 численность граждан Украины, которые подписали декларации с врачами выросла на 1,5 млн., 30 млн. 610 тыс. граждан Украины уже заключили декларации с врачами первичного звена.

На предоставление населению первичной помощи законтрактовано 1682 поставщиков, из которых 1102 – коммунальные учреждения здравоохранения, 206 – частные, 374 – врачи ФЛП. Количество поставщиков первичной помощи, заключивших договор с Национальной службой здравоохранения Украины по состоянию на 01.10.2020 года на 216 больше, чем на конец прошлого года. Причем 75% из них являются частными или врачами ФЛП [10].

Третье направление связано с коренным изменением системы управления здравоохранения. В первую очередь это касается направления закупок медицинских услуг и лекарств, которое предусматривает порядок заключения договоров между Правительством и субъектами хозяйствования. Для реализации этого направления реформы было принято Постановление Кабинета Министров Украины № 1101 от 27 декабря 2017 года, которым утверждено «Положение о

Национальной службе здравоохранения Украины». Данным нормативно-правовым актом установлено, что Национальная служба здравоохранения Украины является центральным органом исполнительной власти, деятельность которого направляется и координируется Кабинетом Министров Украины через Министра здравоохранения, который реализует государственную политику в сфере здравоохранения [8].

Национальная служба здравоохранения Украины является оператором, который заключает контракты на покупку медицинских услуг, а также контракты с медицинскими учреждениями и частными врачами.

В случае реформирования четвертого направления, речь идет об изменениях в фармацевтической отрасли. Таким образом, в соответствии с принятой стратегией реформирования здравоохранения, предлагается отменить обязательную регистрацию в Украине тех препаратов, которые уже прошли сертификацию в ЕС и США. Это поможет снизить цены на лекарства на 30-40%.

Резюмируя вышеперечисленные направления реформы здравоохранения в Украине, следует отметить, что в целом она направлена на создание свободного рынка медицинских услуг. Конечным результатом реализации намеченных мероприятий является перевод отношений в сфере здравоохранения от административной модели к экономической. В частности, это находит свое отражение в создании новой организации по оказанию таких услуг, которая независима в своей финансовой деятельности от исполнительной власти. Если раньше предполагалось, что государство финансирует медицинские учреждения за счет ассигнований, то сегодня создается модель, при которой медицинские учреждения, врачи будут заинтересованы в создании условий, при которых их будет выбирать пациент – потребитель их услуг. То есть создается конкурентоспособная модель оказания медицинских услуг, в основе которой лежат экономические и правовые особенности этих отношений.

Согласно основным положениям реформы системы здравоохранения создаются предприятия экономического типа, целью которых является не только оказание качественных медицинских услуг, но и получение доходов от оказания этих услуг. И чем выше качество такой услуги, тем больше будет потребителей, тем лучше будут условия, зарплата специалистов, которые там работают, и так далее. В таких условиях медицинские учреждения будут конкурировать друг с другом за пациента, поскольку финансирование медицинского учреждения будет происходить не как в советской модели, когда финансировались койки, а за услуги, предоставляемые конкретному пациенту. То есть, теперь медицинское учреждение будет получать финансирование по количеству обслуживаемых пациентов.

Не менее важным нововведением в реформе здравоохранения является договорной характер отношений между врачом и пациентом. Реформа предусматривает возможность гражданину выбрать врача и заключить с ним соответствующий договор. Этот момент положительно отражается на платежной системе, которая стандартизирована, так как определяется средняя стоимость услуги.

Таким образом, подписывая декларацию с желаемым врачом, государство начинает оплачивать медицинское обслуживание этого человека в поликлинике или больнице. По сравнению с предыдущей моделью, новая заключается в том, что Национальная касса медицинского страхования выделяет для каждого отдельного медицинского учреждения сумму, которая формируется на основе количества подписанных деклараций с врачами и в соответствии с установленными тарифами для каждого пациента. Базовый тариф на медицинское обслуживание украинцев в 2020 году составляет 600,48 гривен.

Подводя итог вышеизложенному, можно сказать, что реформа здравоохранения в Украине – это не только необходимость изменения ее советской модели на рыночную модель медицинских услуг, основанную на экономических и правовых принципах, но и требование времени в связи с украинской проевропейской политикой и евроинтеграционными процесами всех сфер государственной деятельности. Однако, как отмечает И. Молен, Украине необходимо выбрать оптимальный вариант модели системы здравоохранения, чтобы добиться результатов на уровне европейских стран [6].

В то же время, следует отметить, что как и любая модель, она не лишена недостатков. Так, например, не был рассмотрен вопрос предоставления медицинских услуг и их оплаты филиалами Национальной академии медицинских наук Украины.

Отраслевые академии наук основаны на государственной собственности, финансируются из Государственного бюджета Украины, а также из других источников финансирования, не запрещенных законодательством Украины. Из Государственного бюджета Украины финансирование отраслевых академий наук осуществляется за счет основного и программно-целевого финансирования. Базовое финансирование Национальной академии наук Украины, отраслевых академий наук обеспечивает фундаментальные научные исследования, развитие инфраструктуры и обновление материально-технической базы научной и научно-технической деятельности, сохранение уникальных научных объектов и объектов, являющихся государственной собственностью, обучение персонала, научных кадров.

Программно-целевое финансирование осуществляется на конкурсной основе в порядке, установленном законодательством Украины. Однако в Концепции реформы финансирования здравоохранения, утвержденной распоряжением Кабинета Министров Украины от 30 ноября 2016 г. № 013-р, не учтены особенности правового статуса деятельности государственных научно-исследовательских учреждений, их уровень управленческой и финансовой автономии, которые могут иметь собственный доход, полученный от оплаты услуг, оказываемых ими в соответствии с основным видом деятельности.

К недостаткам также можно отнести отсутствие единого подхода к определению стоимости медицинских услуг. Одна и та же услуга может отличаться по стоимости в разных медицинских учреждениях, что в современных условиях создает ситуацию, когда пациент, в большинстве случаев, выбирает медицинское учреждение, где услуга оказывается по более низкой цене и, тем самым, препятствует развитию свободной конкуренции.

Заключение. Следует отметить, что международный опыт убедительно демонстрирует эффективность системы, которая способна использовать имеющиеся ресурсы социально ответственным образом, может предоставлять эффективную медицинскую помощь, основанную на солидарности, справедливости и участии общественности, защищать население от катастрофических последствий болезней, гарантирует прозрачность и подотчетность. Принятие мер для более быстрого реагирования на потребности и ожидания населения требует более тесной связи между развити-

ем национальной экономики и благосостоянием граждан. Переход системы здравоохранения от административно-командной к рыночной модели оказания медицинских услуг на экономической и правовой основе в целом является положительным шагом в выборе направления реформы. Однако реформа здравоохранения в Украине находится только на начальной стадии. Нелегко изменить систему, которая строилась десятилетиями и укоренилась в сознании большинства населения страны. Процесс реформирования не должен ограничиваться принятием только законодательной базы, а обусловлен также необходимостью научного и общественного обсуждения. В связи с этим, возникает необходимость дальнейших исследований с целью выработки общих теоретических и практических позиций.

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SUMMARY

CURRENT STATE OF HEALTH REFORM IN UKRAINE IN THE CONDITIONS OF EUROPEAN INTEGRATION

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The problem of health is one of the global problems, the solution of which contributes to the further development of the state. The article is devoted to topical issues of medical reform implementation in Ukraine. The importance of making changes in the field of medicine is analyzed. The main problems and obstacles to the introduction of new principles of interaction are considered.

The purpose of the study is to identify the most pressing problems of health care reform, to determine the essence of health care reform, to indicate its possible pros and cons.

To achieve this goal, an analysis of the regulatory and legal framework for reforming the healthcare sector in Ukraine was carried out, the stages of reform that have already been completed to date and those that are still in the process of implementation, their positive and negative aspects were analyzed, methods were used: comparative legal, statistical, induction, analysis, synthesis.

Based on the study, the authors concluded that the transition of the health care system from an administrative-command to a market model of medical services on an economic and legal basis is generally a positive step in choosing the direction of reform. The main fundamental principles envisaged by the reform are: the responsibility of the state, the availability and quality of medical services, the convenience of obtaining them, ensuring equal access to services and efforts to make the most efficien use of available resources.

Keywords: medical system, medical reform, stages of medical reform, financing, health insurance

РЕЗЮМЕ

СОВРЕМЕННОЕ СОСТОЯНИЕ РЕФОРМЫ ЗДРАВООХРАНЕНИЯ В УКРАИНЕ В УСЛОВИЯХ ЕВРОИНТЕГРАЦИИ

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Проблема здоровья относится к глобальным проблемам, решение которых способствует дальнейшему развитию нашего государства. Статья посвящена актуальным вопросам внедрения медицинской реформы в Украине. Анализируется важность проведения изменений в сфере медицины. Рассматриваются основные проблемы и препятствия внедрения новых принципов взаимодействия.

Цель исследования заключается в том, чтобы выявить наиболее актуальные проблемы медицинского реформирования, определить сущность медицинской реформы, выделить возможные её плюсы и минусы.

Для реализации поставленной цели был проведен анализ нормативно-правовой базы реформирования сферы здравоохранения в Украине, проанализированы этапы реформирования, которые уже выполнены на сегодня и те, которые еще в процессе выполнения, их положительные и отрицательные моменты, использованы методы: сравнительно-правовой, статистический, индукции, анализа, синтеза.

На основании проведенного исследования авторами сделан вывод о том, что переход системы здравоохранения от административно-командной к рыночной модели предоставления медицинских услуг на хозяйственно-правовых основах в целом является положительным шагом в выборе направленности реформы. Основными фундаментальными принципами, которые предусматриваются реформой явля-

ются: ответственность государства, доступность и качество медицинской услуги, удобство ее получения, обеспечения равенства в доступе к услугам и попытки наиболее эффективно использовать имеющиеся ресурсы.

რეზიუმე

ჯანმრთელობის დაცვის რეფორმის თანამედროვე მდგომარეობა უკრაინაში ევროინტეგრაციის პირობებში

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ჯანმრთელობის პრობლემა მიეკუთვნება გლობალურ პრობლემებს, რომელთა გადაწყვეტა ხელს უწყობს ჩვენი სახელმწიფოს შემდგომ განვითარებას. სტატია ეძღვნება სამედიცინო რეფორმის დანერგვის აქტუალურ საკითხებს უკრაინაში. ხდება ცვლილებების ჩატარების საჭიროების გაანალიზება მედიცინის სფეროში. განიხილება ურთიერთობის ახალი პრინციპების დანერგვის ძირითადი პრობლემები და წინააღმდეგობები.

გამოკვლევის მიზანი მდგომარეობს იმაში, რომ გამოვლენილ იქნეს სამედიცინო რეფორმირების უფრო მეტად აქტუალური პრობლემები,განსაზღვრულ იქნეს სამედიცინო რეფორმის არსი, გამოიყოს მისი შესაძლო პლიუსები და მინუსები.

დასახული მიზნის რეალიზაციისთვის ჩატარებულ იქნა ჯანდაცვის სფეროს რეფორმირების ნორმატიულ-სამართლებრივი ბაზის ანალიზი უკრაინაში, გაანალიზებულია რეფორმირების ეტაპები, რომელიც უკვე შესრულებულია დღეისათვის და ის ეტაპები, რომელიც ჯერ კიდევ შესრულების პროცესშია, მათი დადებითი და უარყოფითი მომენტები, გამოყენებულია ხერხები: შედარებითი და სამართლებრივი, სტატისტიკური, ინდუქციის, ანალიზის, სინთეზის.

ჩატარებული კვლევის საფუძველზე ავტორების მიერ გაკეთებულია დასკვნა იმის შესახებ, რომ ჯანდაცვის სისტემის გადასვლა ადმინისტრაციულ-გუნდურიდან სამედიცინო მომსახურებათა გაწევის საბაზრო მოდელზე სამეურნეო-სამართლებრივ საფუძვლებზე მთლიანობაში წარმოადგენს დადებით ნაბიჯს რეფორმის მიმართულების არჩევაში.

ძირითადი ფუნდამენტური პრინციპები, რომელსაც ითვალისწინებს რეფორმა არის: სახელმწიფოს პასუხისმგებლობა, სამედიცინო მომსახურების ხელმისაწვდომობა და ხარისხი, მისი მიღების მოხერხებულობა, წვდომაზე თანასწორობის უზრუნველყოფა მომსახურებაში და არსებული რესურსების უფრო მეტად ეფექტიანად გამოყენების ცდები.

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