ПЕРМСКИЙ
МЕДИЦИНСКИЙ
УНИВЕРСИТЕТ АКАДЕМИКА ВАГНЕРА
1916

PERM MEDICAL JOURNAL

2' 2024
vol. 41

SCIENTIFIC AND PRACTICAL PUBLICATION

Perm Medical Journal

ISSN 0136-1449 (Print)
ISSN 2687-1408 (Online)

VOLUME 41

2'2024

16+

SCIENTIFIC AND PRACTICAL REFERRED JOURNAL

Founder:
Federal State Budgetary
Educational Institution of Higher Education
"E.A. Vagner Perm State Medical University"
of the Ministry of Health of the Russian Federation

"Perm Medical Journal" is a peer-reviewed scientific and practical journal. It was founded in 1923 by Medical Society of Perm University. Since 2001, the founders of "Perm Medical Journal" are Perm State Academy of Medicine and Perm Research Centre of RAMS and Administration of Perm Region. Since 2017, the founder is Academician E.A. Vagner Perm State Medical University.

The journal is registered by the Ministry of the Russian Federation for Press, Television and Radio Broadcasting and Mass Communications (PI №77-12317, 02.04.2002).
In 2017 the journal was re-registered by the Federal Service for Supervision in the Sphere of Communication, Information Technologies and Mass Communications (Rospotrebnadzor) (Registration certificate of mass medium (PI № FS 77 – 70264,13.07.2017).

Published with financial support from the Ministry of Education and science of the Perm region.

The journal is included in the following databases: Scopus, EBSCO, RSCI, VAK, WorldCat, Google Scholar, Ulrich's Periodical Directory, CyberLeninka

Distribution territory:
Russian Federation, foreign countries

Founder, publisher and editorial office address:
26 Petropavlovskaya st., Perm 614990
Executive secretary – I.A. Bulatova
Tel (342) 217-19-38
Fax (342) 217-20-21
E-mail: permmedjournal@psma.ru
Web-site: https://permmedjournal.ru

Пермский медицинский журнал

ISSN 0136-1449 (Print)
ISSN 2687-1408 (Online)

ТОМ 41

2'2024

16+

НАУЧНО-ПРАКТИЧЕСКИЙ РЕЦЕНЗИРУЕМЫЙ ЖУРНАЛ

Учредитель:
Федеральное государственное бюджетное образовательное учреждение высшего образования «Пермский государственный медицинский университет имени академика Е.А. Вагнера» Министерства здравоохранения Российской Федерации.

«Пермский медицинский журнал» – рецензируемый научно-практический журнал. Основан в 1923 году Медицинским обществом при Пермском университете. С 2001 года учредителями «Пермского медицинского журнала» являются Пермская государственная медицинская академия и Пермский научный центр РАМН и администрации Пермской области. С 2017 года – учредитель Пермский государственный медицинский университет имени академика Е.А. Вагнера.

Журнал зарегистрирован в Министерстве Российской Федерации по делам печати, телерадиовещания и средств массовых коммуникаций (ПИ № 77-12317 от 02.04.2002 г.).
В 2017 году журнал прошел перерегистрацию в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор) (Свидетельство о регистрации средства массовой информации ПИ № ФС 77 – 70264 от 13.07.2017).

Издается при финансовой поддержке Министерства образования и науки Пермского края.

Входит в базу данных Scopus, EBSCO, РИНЦ, ВАК, WorldCat, Google Scholar, Ulrich's Periodical Directory, CyberLeninka

Территория распространения:
Российская Федерация, зарубежные страны

Адрес учредителя, издателя и редакции:
614990, Пермский край, г. Пермь, ул. Петропавловская, д. 26
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Scientific Article
UDC 615.281.03: 616-9-022.369: 579.861.2.] 015.8
DOI: 10.17816/pmj4125-10

ANALYSIS OF LONG-TERM DYNAMICS OF ANTIBIOTIC SENSITIVITY OF COAGULASE-NEGATIVE STAPHYLOCOCCI ISOLATED FROM SURGICAL HOSPITAL PATIENTS AT VARIOUS TIMES

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АНАЛИЗ МНОГОЛЕТНЕЙ ДИНАМИКИ АНТИБИОТИКОЧУВСТВИТЕЛЬНОСТИ КОАГУЛАЗООТРИЦАТЕЛЬНЫХ СТАФИЛОКОККОВ, ИЗОЛИРОВАННЫХ В РАЗЛИЧНЫЕ СРОКИ ОТ ПАЦИЕНТОВ ХИРУРГИЧЕСКОГО СТАЦИОНАРА

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Objective. To carry out twenty-year analysis of dynamics of antibiotic sensitivity of coagulase-negative staphylococcal strains isolated from surgical hospital patients.

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Materials and methods. The antibiotic sensitivity of 191 strains of coagulase-negative staphylococci isolated in 2004, 2014, 2023 year from surgical hospital patients was studied with the disk diffusion method.
Results. A significant increase in the proportion of strains resistant to all antibiotics known, especially ciprofloxacin, was found.
Conclusion. A twenty-year analysis of the dynamics of antibiotic sensitivity showed a significant increase of antibiotic resistance of coagulase-negative staphylococcus strains isolated from surgical patients.
Keywords. Antibiotic sensitivity, coagulase-negative staphylococci, antibiotic resistance.

Цель. Многолетний анализ динамики антибиотикочувствительности штаммов коагулазоотрицательных стафилококков, изолированных от пациентов хирургического стационара.
Материалы и методы. Изучена антибиотикочувствительность 191 штамма коагулазоотрицательных стафилококков, изолированных в 2004, 2014, 2023 гг. от пациентов хирургического стационара. Чувствительность изолятов к антибиотикам определяли диско-диффузионным методом.
Результаты. В процессе наблюдения установлено значительное увеличение доли антибиотикорезистентных штаммов, что было характерно по отношению ко всем изученным препаратам, особенно существенно к ципрофлоксацину.
Выводы. Двадцатилетний анализ показал существенный рост антибиотикорезистентности штаммов коагулазоотрицательных стафилококков, изолированных от больных хирургического профиля.
Ключевые слова. Антибиотикочувствительность, коагулазоотрицательные стафилококки, антибиотикорезистентность.

INTRODUCTION

Staphylococci are widespread in nature. They inhabit various biotopes of the human and animal body, can be found in the air, water, and on household items [1]. These microorganisms are characterized by a pronounced species diversity. There are more than 45 species currently known. Traditionally, bacteria of the *Staphylococcus* genus are classified as conditionally pathogenic microorganisms. Meanwhile, they can cause a wide variety of infectious and inflammatory diseases, from the ordinary purulent processes to severe pneumonia and sepsis [1–3]. This diversity of infectious nosology is appreciably explained by the polytropic character of staphylococci. The aetiological role of these microorganisms in the development of healthcare associated infectious (HAIs) and inflammatory diseases is of a particular significance [2; 3].

Previously, the main cause of staphylococcal infections was only considered to be bacteria of one type – *S. aureus*. Representatives of this type of staphylococci have been the main causative agents of various purulent infections of surgical wounds for more than a hundred years [4]. In recent years, coagulase-negative staphylococci (CoNS) have become more and more common as aetiological agents of such diseases. [5]. They cause a significant number of HAIs. Treatment of such diseases is significantly difficult, since CoNS strains circulating in hospitals are usually characterized by high antibiotic resistance [6; 7]. At the moment, the problem of resistance of staphylococci to chemopreparations is becoming increasingly relevant.

Methicillin-resistant CoNS strains are often isolated from patients in surgical hospitals, which is due to the synthesis of penicillin – binding protein (target change mechanism). Strains that are resistant to carbapenems and other modern antibacterial drugs are also frequently isolated [8; 9]. Their source can be both medical personnel and patients undergoing treatment in an inpatient department [10; 11]. At the same time, the number of pandrug-resistant strains of CoNS – pathogens of HAIs – is steadily increasing [5; 6].

The objective of the study was a long-term analysis of the dynamics of antibiotic sensitivity of coagulase-negative staphylococcal strains isolated from surgical hospital patients.

MATERIALS AND METHODS

The antibiotic sensitivity of 191 CoNS strains isolated from the wound effluent of surgical patients with various infectious and inflammatory complications developed after thoracic surgery was studied in a comparative aspect, including: 62 strains in 2004; 48 – in 2014; 81 – in 2023. Pure cultures were isolated and identified using the classical bacteriological method. The sensitivity of isolates to antibiotics was studied using the traditional disk diffusion method on Givental-Vedmina (2004) and Muller-Hinton (2014, 2023) agar. Inoculation, recording of the results obtained, and selection of test preparations were carried out in accordance with methodological guidelines MUK 4.2.1890-04 "Determination of the sensitivity of microorganisms to antibacterial drugs". The main groups of antibiotics used were oxacillin/ceftazidime (β-lactams), erythromycin (macrolides), gentamicin (aminoglycosides), lincomycin (lincosamides), thienam (carbapenems), ciprofloxacin (fluoroquinolones). The proportion of sensitive strains was expressed as a percentage.

RESULTS AND DISCUSSION

CoNS strains isolated from surgical hospital patients at various times were of a fairly wide species diversity: *S. epidermidis, S. varneri, S. saprophyticus, S. cochnii, S. hominis, and S. chromogenes*. However, in the vast majority of cases (from 78 to 90 %), the wound effluent contained cultures of *S. epidermidis*, while representatives of other species were detected in isolated cases. In this regard, we further considered it possible to group all such isolated strains together under the term "CoNS". Since earlier antibiotics were periodically rotated in medical institutions, when studying the antibiotic sensitivity of isolated strains, we only used the drugs that were used at all the specified reference points. The results obtained are shown in the table.

It follows from the received data that the proportion of sensitive strains isolated from patients in 2004 was higher. Further – in 2014 and especially in 2023 – the proportion of resistant strains increased. This trend was characteristic for practically all tested antibiotics.

Results of studying the antibiotic sensitivity of CoNS strains isolated from surgical hospital patients at different periods of observation

Reference points, years	Proportion of antibiotic-resistant CoNS strains, %					
	oxacillin/ ceftazidime	gentamicin	erythromycin	lincomycin	thienam	ciprofloxacin
2004	15.91	7.8	14.3	8.6	1.4	9.8
2014	19.4	35.7	21.2	21.0	7.4	35.7
2023	38.2	36.4	44.1	17.6	21.1	98.0

It was specifically evident in the case of ciprofloxacin (fluoroquinolones). While in 2004, only 9.8 % of bacterial strains were resistant to this antibiotic, by 2023, this number had increased to 98 %.

As for the antibacterial activity of certain drugs, thienam was the most effective in all observation periods. Thus, 1.4 % of strains were resistant to it in 2004, while 7.4 % and 21.1 % appeared to be resistant in 2014 and 2023, respectively.

It should be noted that the antibiotic resistance of the studied CoNS strains increased. Thus, after the first 10 years from the beginning of observation, the proportion of resistant strains increased slightly. This applies essentially to all tested drugs, except gentamicin. Subsequently, from 2014 to 2023, the antibiotic resistance of CoNS strains increased several times over. It can be assumed that the accumulation of antibiotic-resistant strains circulating in the healthcare institutions in recent years is largely due to the widespread use of antibiotics during the COVID-19 pandemic, when they were used for the prevention and treatment of bacterial complications.

The analysis of the resistance of CoNS strains to methicillin in different periods of observation is of certain interest, since, as is known, the resistance of bacteria to this drug indicates their resistance to β-lactam antibiotics. Over time, an increase in the proportion of resistant strains to this drug was also observed. Thus, in 2004 there were 2.8 % of them, while in 2014 their number increased up to 21 %, and up to 38 % – in 2023. At the same time, among methicillin-resistant staphylococci, some multidrug resistant cultures resistant to three or more antibiotic drugs were detected significantly more often.

CONCLUSION

A twenty-year analysis of the dynamics of changes in the antibiotic sensitivity of CoNS strains isolated from patients with infectious and inflammatory complications that occurred after thoracic surgery showed a significant increase in the antibiotic resistance of these bacteria, especially to ciprofloxacin. The number of methicillin-resistant strains also increased significantly. These circumstances should

be taken into account in the treatment of emerging postoperative complications. The administration of certain antibacterial drugs should be preceded by an investigation of the antibiotic sensitivity of isolated aetiopathogens.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 12/03/2023
Revised version received: 12/26/2023
Accepted: 03/15/2024

Please cite this article in English as: Afanasievskaya E.V., Kasatov A.V., Nikolaeva N.V., Pospelova S.V. Analysis of long-term dynamics of antibiotic sensitivity of coagulase-negative staphylococci isolated from surgical hospital patients at various times. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 5-10. DOI: 10.17816/pmj4125-10

Scientific Article
UDC 006.617-089
DOI: 10.17816/pmj41211-18

MODERN METHODS OF TREATMENT OF ANAL STENOSIS

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СОВРЕМЕННЫЕ МЕТОДЫ ЛЕЧЕНИЯ АНАЛЬНЫХ СТЕНОЗОВ

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Objective. To develop and put into practice a new combined method of anal stenosis surgical treatment based on laser plastic surgery of tissues with a diode laser. Assess the effectiveness of the technique based on the analysis of immediate and long-term results, postoperative complications, peculiarities of technical implementation, and features of the quality of patients` life.

Materials and methods. The study involved 68 patients with anal stricture after the anal and (or) rectal surgery. All patients underwent laser correction of postoperative scar tissue. According to indications, botulinum toxin was injected into the internal sphincter and (or) PRP autoplasma perarectally. Surgery was performed under intravenous anesthesia with the addition of tumescent anesthesia or local anesthesia. Laser radiation from a diode device with a wavelength of 1.56 microns and a power of 10 W was applied.

Results. There are no restrictions on laser correction of anal stenosis regardless of the type and complexity of anal stenosis, it is technically easy to use, minimizes the risk of postoperative complications and relapse of the disease, and has a highly effective treatment result.

Conclusions. The technique is characterized by versatility and ease of use, highly effective results, high quality of patients` life, and it can be used routinely on an outpatient basis.

Keywords. Anal stenosis, anal stricture, laser, botulinum toxin, PRP autoplasma.

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Цель. Разработать и внедрить в практику новую комбинированную методику хирургического лечения анального стеноза, основанную на лазерной пластике тканей диодным лазером. Провести оценку эффективности методики, основываясь на анализе ближайших и отдаленных результатов, наличии послеоперационных осложнений, особенностях технического выполнения и качества жизни пациентов.

Материалы и методы. В исследовании приняли участие 68 пациентов с анальной стриктурой после хирургического лечения анального канала и (или) прямой кишки. Всем пациентам выполнялась лазерная коррекция послеоперационной рубцовой ткани. По показаниям вводился ботулинический токсин во внутренний сфинктер и (или) PRP-аутоплазма параректально. Хирургическое лечение выполнялось под внутривенным обезболиванием с добавлением тумесцентной анестезии или под местной анестезией. Применялось лазерное излучение диодного аппарата с длиной волны 1,56 мкм, мощность – 10 Вт.

Результаты. Лазерная коррекция анального стеноза не имеет ограничений по виду и сложности анального стеноза, обладает технической простотой в применении, позволяет минимизировать риск послеоперационного осложнения и рецидива заболевания, обладает высокой эффективностью результата лечения.

Выводы. Методика характеризуется универсальностью и простотой применения, высокой эффективностью результата, высоким качеством жизни пациентов, может применяться рутинно в амбулаторных условиях.

Ключевые слова. Анальный стеноз, анальная стриктура, лазер, ботулинический токсин, PRP-аутоплазма.

INTRODUCTION

Anal stenosis continues to be a relevant problem in modern coloproctology. Acquired anal stenoses, also known as strictures, develop in 90 % of cases after surgery performed on the anal canal [1]. The incidence rate, according to various data, ranges from 1.5 to 9 % among all operated patients with benign diseases of the rectum and anal canal [2].

Predisposing factors for the development of anal stenosis are autoimmune diseases, pathology of the gastrointestinal tract, the presence of food or drug allergies, abdominal and pelvic adhesions, rapid acetylation, an increase in the number of positive reactions of the test system with an antigenic scar complex and blood sera of patients in dynamics. These factors result in increased formation of excessive dense scar tissue in patients after anal canal surgery [3].

The main cause of anal canal strictures is an excessive amount of surgical intervention. Another common cause is the development of purulent-septic complications in the postoperative period [4].

Treatment of anal stenosis depends on the severity of scarring. In mild cases of stenosis, conservative treatment is recommended. There are some methods of bougienage and divulsion with the use of cones of various diameters, pneumodilators, etc. [5]. Moderate to severe strictures require surgical treatment. Modern medicine describes many methods of surgical treatment of anal stenosis, most of them are plastic surgery.

The most common complication of surgical treatment is anal insufficiency (up to

39 %). Moreover, postoperative bleeding, necrosis, suppuration, long-term non-healing wounds (up to 18 %) may occur. The relapse rate of the disease reaches 25 % [6].

Anal plastic surgery techniques have several main variants and their modifications, e.g. Y-V anoplasty, diamond flap anoplasty, house advancement flap anoplasty, island flap anoplasty, anoplasty with internal sphincterotomy, etc. [7–10]. Postoperative complications are caused by the complexity of the healing process of the anal canal due to the high level of displacement of the tissues of anus with their defecation trauma and a constant high level of bacterial contamination of postoperative wounds. Apart from that, anal stenosis always implies a weakened vascular microcirculation with a decreased level of oxygenation in scar tissue.

To improve the effectiveness, all types of anoplasty and sphincterotomy are currently performed selectively for each patient according to individual indications and often in combination. However, even under these conditions, the complication rate is determined to be no less than 13 %, and the relapse rate is no less than 7 % [11–15].

The objective of the study was to develop and put into practice a new combined method of anal stenosis surgical treatment based on laser plastic surgery of tissues with a diode laser. Assess the effectiveness of the technique based on the analysis of immediate and long-term results, postoperative complications, peculiarities of technical implementation, and features of the quality of patients' life.

MATERIALS AND METHODS

The study included 68 patients with anal stricture who underwent surgery between 2018 and 2023. The exclusion criteria were severe somatic condition of patients, a recent stroke or acute myocardial infarction (less than 3 months before the study), decompensated diabetes mellitus, and renal or hepatic insufficiency. The patients were conditionally divided into three groups according to the degree of narrowing – mild, moderate, and severe. The degrees directly correlated with the level of scar changes, the amount of surgical treatment, and the difficulties of postoperative rehabilitation (Table 1).

Table 1

Distribution of patients by gender and degree of disease

Stage	Male, abs (%)	Female, abs (%)
Mild	14 (45.2)	21 (56.8)
Moderate	13 (41.9)	14 (37.8)
Severe	4 (12.9)	2 (5.4)
Total	31 (100)	37 (100)

All the studied patients underwent laser correction of the scar tissue of the anal canal and/or lower ampullary rectum. Large keloid scars were subjected to interstitial destruction, and the superficial scar tissue was punctually treated by external influence. The radiation power in all cases was 10 W, the impulse mode was 0.5/0.5 s. The duration of exposure during the proce-

dure is no more than 1 second at one point with interstitial exposure and about 0.5 seconds with superficial treatment of less dense tissues. The distance between adjacent impact points averaged approximately 2 mm. The treatment was carried out under visual control of a pilot light indicator, and the intensity of the impact was also visually evaluated by changing the color of the scar tissue from white to yellow-gray. The appearance of darker shades indicates the beginning of carbonation (ablation) of tissues, which creates conditions for the development of postoperative complications. In the presence of an anal fissure in the scar tissue, the treatment was similar. To assess the functional state of the obturator apparatus, the first 12 operated patients underwent anorectal manometry (sphincterometry) 3–4 months after the surgery. In the remaining 56 patients, the study was not performed due to positive data previously obtained in 12 patients and based on the absence of functional complaints among all operated patients. In order to prevent postoperative spasm and improve vascular tissue nutrition, 43 of these 56 patients were intraoperatively injected with botulinum toxin at a dose of 50 IU into the internal sphincter. In 7 patients, long-term healing of postoperative wounds was noted – more than 2 months. PRP autoplasma was administered perarectally for correction, and a positive result was recorded in all cases (Table 2).

The majority of surgical interventions (65 patients) were performed under intravenous anesthesia with the addition of tumescent anesthesia. In 3 cases, at the request of the patients, the interventions were performed under local infiltration anesthesia. All the patients were admitted to a day hospital after the operation. Follow-up examinations were performed at two weeks, one, three and twelve months after the surgery.

The results were assessed based on the severity and duration of postoperative pain syndrome, the period of wound regeneration, the presence of postoperative complications and relapse of the disease, as well as the patient's satisfaction with the performed treatment.

RESULTS AND DISCUSSION

The treatment outcomes were evaluated at one, three, and twelve months after the surgery. Results were tracked in all 68 patients (100 %) within these terms.

Pain syndrome was assessed according to the VAS scale. All the patients had a one-time intraoperative administration of ketorolac (30 mg). Additional anesthesia was not required in any case. The period of hospitalization for all the patients was up to 5 hours. In the postoperative period, NSAIDs of the class of selective COX inhibitors were prescribed (Table 3).

The pain syndrome was not pronounced in all the cases – it depended on the stool, so the patients usually did not need additional anesthesia outside of defecation. One week after the surgery, the vast majority did not take any painkillers. However,

Table 2

Combinations of laser treatment, botulinum toxin and PRP autoplasma injection

Degree of stenosis	Laser, abs. (%)	Botulinum toxin, abs. (%)	Autoplasma, abs. (%)
Mild	35 (51.5)	18 (26.4)	–
Moderate	27 (39.7)	22 (32.4)	4 (5.9)
Severe	6 (8.8)	3 (4.4)	3 (4.4)
Total	68 (100)	43 (63.2)	7 (10.3)

Table 3

VAS scale pain syndrome assesment

Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Pain syndrome (points)	3.1+/-0.5	2.6+/-0.4	2.4+/-0.3	2.2+/-0.4	2.1+/-0.5	1.8+/-0.3	1.6+/-0.2
Taking NSAIDs, abs. (%)	68 (100)	62 (91.2)	58 (85.3)	52 (76.5)	43 (63.2)	31 (45.6)	17 (25)

according to our observations, some slight discomfort after stool persisted in all the patients for at least 1.5 months after surgical treatment. In some cases, the sensation post-defecation discomfort persisted for up to 6 months without any signs of objective pathological changes in the anal canal. They were of a low intensity and did not require additional anesthesia.

Complications in the immediate postoperative period, such as suppuration, sphincter spasm, and acute urinary retention, were not observed. Bleeding was recorded in one case. It was detected one week after the surgical treatment and was expressed by the daily discharge of 20–30 ml of blood during defecation. Defecation was complicated due to transient weakness of the muscular apparatus, blood was discharged from defects in the anoderm, and it was eliminated by stitching the anoderm with two separate sutures under local anesthesia.

At the beginning of our work, we observed a mild degree transient anal insufficiency in the form of periodic poor gas retention and nocturnal scanty discharge of intestinal mucus for about a month after the surgery. Therefore, we performed sphincterometry (anorectal manometry) in the first 12 patients to assess the function of the obturator apparatus and determine further patient management tactics. Sphincterometry was performed 2–3 months after the surgery and depended on the healing time of postoperative wounds and the absence of pain. However, by the end of the second month after the surgery, subjective complaints of lack of tightness in the anus disappeared in all patients. The conducted studies revealed the absence of anal insufficiency manifestations (Table 4).

The healing time of postoperative wounds ranged from 6 to 20 weeks. They directly correlated with the severity of scarring (Table 5).

Table 4

Anorectal manometry

Male, $n = 4$		Female, $n = 8$	
Average resting pressure, mmHg	Maximum contraction pressure, mmHg	Average resting pressure, mmHg	Maximum contraction pressure, mmHg
44–53	124–178	44–53	124–178

Table 5

Absence of complete healing of postoperative wounds

Degree of stenosis	6 weeks, abs. (%)	12 weeks, abs. (%)	18 weeks, abs. (%)
Mild	29 (42.6)	–	–
Moderate	15 (22.1)	1 (1.5)	–
Severe	6 (8.8)	6 (8.8)	2 (4.4)
Total	68 (100)	43 (63.2)	7 (10.3)

Cases of absence of complete epithelialization of wounds for more than 12 weeks were classified as complications – long-term non-healing wounds.

All the patients were evaluated for retention function after one year on the Wexner scale. In all the cases, no disturbance was detected (0 points). In the postoperative period, all the patients were recommended doing Kegel exercises at least 2 times a day for a period of no less than 3 months for preventive purposes after the pain and discomfort subsided.

In the long-term postoperative period, along with the function of the locking device, we evaluated the presence of long-term non-healing wounds and relapses of the disease 3 and 12 months after the surgery. After 3 months, epithelialization was not achieved in 7 patients (10.3 %), periodic discomfort was observed in 18 people (26.5 %). After 12 months, there were no defects in healing and no cases of significant discomfort for the patient.

All the patients with long-term non-healing wounds were from the group of severe stenoses. In all of the cases, we performed repeated laser treatment of the wound defect with an end light guide under local anesthesia, combining it with perarectal autoplasma injection and local application of collagen dressings. In the period of up to 2 months after the performed manipulations, the wounds were epithelized in all of the cases.

The evaluation of the quality of life was carried out at 1 and 12 months after the treatment. In all of the cases, patients noted a significant improvement in the quality of life on the second day of the postoperative period and characterized the results as good (13.5 %) and excellent (76.5 %).

Laser correction of anal stenosis has little experience of application. However, the obtained results indicate its high efficiency

and safety. Treatment of scar tissue with laser radiation at a power of 10W in pulse mode allows punctual and detailed elimination of scarring changes under visual control, while in the healing process of wound surfaces, due to the optimal ratio of type I and III collagens, not rigid, but elastic fibrous tissue is formed, that is close in its properties to the normal mucosa of the anal canal. This allows the anal canal to regain its elastic properties in the postoperative period.

The combination of laser treatment with the introduction of botulinum toxin into the internal sphincter accelerates the healing processes by improving tissue oxygenation. In cases of massive scarring processes with long-term wound healing, the regeneration process is effectively stimulated by perarectal administration of PRP-autoplasma. Minimally invasive methods and the possibility of a combined individual approach create conditions for minimizing the risks of postoperative complications and ensure the patient's recovery without the risk of developing a relapse of the disease.

Conclusion

The developed method of surgical treatment of anal stenosis is highly effective – in all of the cases, a positive treatment result was achieved. It is safe to apply – from the recorded complications, there was a single weakly expressed bleeding and about 10 % of cases of long-term non-healing wounds. The discharge of blood did neither require any emergency measures nor pose any risks to the patient's life and health. Long-term non-healing wounds were epithelized in all of the cases by repeated laser treatment of wound surfaces with perarectal autoplasma administration and the application of collagen dressings in the form of local treatment. The pain syndrome had a low intensity and duration in the postoperative period. All the patients reported a significant improvement in their quality of life and rated the treatment results as excellent and good. The performing technique is simple, convenient and fast, has no restrictions on the degree and severity of stenosis, and can be performed on an outpatient basis, under local anesthesia in particular. Laser plastic surgery is a worthy replacement for surgical anoplasty in solving the complex problem of anal stenosis.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

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Cherepenin M.Yu., Lutkov I.V. – collection of material.

Lutkov I.V., Cherepenin M.Yu., Gorsky V.A. – material processing.

Lutkov I.V., Cherepenin M.Yu., Gorsky V.A. – statistical processing.

Lutkov I. V. – writing the text.

Cherepenin M.Yu., Gorsky V.A. – editing.

Received: 11/22/2023
Revised version received: 13/12/2023
Accepted: 03/15/2024

Please cite this article in English as: Cherepenin M.Yu., Lutkov I.V., Gorsky V.A. Modern methods of treatment of anal stenosis. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 11-18. DOI: 10.17816/pmj41211-18

Scientific Article
UDC 616-006.04: 159.9.072: 614.2
DOI: 10.17816/pmj41219-32

REHABILITATION POTENTIAL IN PATIENTS WITH PROSTATE CANCER: PSYCHOLOGICAL ASPECT

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РЕАБИЛИТАЦИОННЫЙ ПОТЕНЦИАЛ У БОЛЬНЫХ РАКОМ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ: ПСИХОЛОГИЧЕСКИЙ АСПЕКТ

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Objective. To determine a list of psychological characteristics associated with the prognosis of prostate cancer outcome and rehabilitation potential in patients with cancer.
Materials and methods. The study of psychological characteristics (subjective and personal characteristics of study participants ($n = 148$)) associated with rehabilitation potential was carried out using the following psychological methods: Methodology of Subjective Control Level (E.F. Bazhin, E.A. Golynkina, L.M. Etkind), Questionnaire of ways to cope (adapted by T.L. Kryukova, E.V. Kuftyak, M.S. Zamyshlyaeva), Questionnaire SF-36 "Assessment of the quality of life", Test of vitality (adapted by D.A. Leontiev, E.I. Rasskazova), Basic Beliefs Scale (adapted by M.A. Padun, A.V. Kotelnikova).
Results. A favorable prognosis for the outcome of prostate cancer is associated with the patient`s involvement in the events of his life and active participation in them, understanding of the significance of the problem, partial independence from others, slight limitation of role functioning due to the emotional state, optimal social functioning in combination with beliefs about the benevolence of the world around him and ability to control events.
Conclusions. A list of psychological characteristics associated with the course of the disease in patients with prostate cancer was obtained. These psychological characteristics can define the rehabilitation potential, being associated with the possibilities of recovery after antitumor treatment.
Keywords. Prostate cancer, rehabilitation potential, prognosis of cancer outcome, course of the disease.

Цель. Определить перечень психологических характеристик, связанных с прогнозом исхода рака предстательной железы, а также реабилитационным потенциалом у онкологических больных.
Материалы и методы. Исследование психологических характеристик (субъектных и личностных характеристик участников исследования ($n = 148$)), связанных с реабилитационным потенциалом, производилось следующими психодиагностическими методикам: методика уровня субъективного контроля (Е.Ф. Бажин, Е.А. Голынкина, Л.М. Эткинд), опросник способов совладания (адаптация Т.Л. Крюковой, Е.В. Куфтяк, М.С. Замышляевой), опросник SF-36 «Оценка качества жизни», тест жизнестойкости (адаптация Д.А. Леонтьева, Е.И. Рассказовой), шкала базисных убеждений (адаптация М.А. Падун, А.В. Котельниковой).
Результаты. Благоприятный прогноз исхода рака предстательной железы связан с вовлеченностью онкобольного в события его жизни и активным участием в них, пониманием значимости проблемы, частичной независимостью от окружающих, незначительным ограничением ролевого функционирования, обусловленного эмоциональным состоянием, оптимальным социальным функционированием в совокупности с убеждениями о доброжелательности окружающего мира и возможности контролировать происходящие события.
Выводы. Получен перечень психологических характеристик, связанных с течением болезни у пациентов с раком предстательной железы. Данные психологические характеристики могут характеризовать реабилитационный потенциал, ассоциируясь с возможностями восстановления после противоопухолевого лечения.
Ключевые слова. Рак предстательной желез, реабилитационный потенциал, прогноз исхода рака, течение болезни.

INTRODUCTION

Modern Russian clinical guidelines for the treatment of patients with cancer currently contain the section "Rehabilitation", which separately describes its stages. This includes pre-rehabilitation as well as the rehabilitation of the 1st, 2nd and 3rd stages. Psychological, including social, rehabilitation of patients with malignant neoplasms is a system of measures implemented in stages and aimed at psychological and social adaptation, starting from establishing the diagnosis, treatment and ending with the

period of recovery [1]. The detection of cancer in a patient, the course of treatment, and the period of remission are usually accompanied by severe psychological issues and feeling of distress, which are closely related and affect all spheres of life. At the same time, various psychosocial needs of patients and their personal experience require a selective approach to identifying people, who need psychological assistance according to the level of adaptive potential.

In rehabilitation practice, aimed at restoring the biopsychosocial status, such a prognostic characteristic as rehabilitation potential is used [2]. Rehabilitation potential is defined as a complex of biological and psychological characteristics of a person, as well as socio-environmental factors that allow to realize their potential abilities to some extent [3]. The central principle of cancer rehabilitation is to help the patients recover and improve their physical, psychosocial, and professional functioning within the constraints imposed by the disease and its treatment. Due to the rising survival rate of oncological patients, issues related to the quality of life are becoming increasingly important [4]. Many consequences of antitumor treatment and complications of an oncological disease can be alleviated through the implementation of rehabilitation measures. [5].

Methods and technologies of providing care for oncological patients continue to develop [6]. New hormonal and chemotherapeutic agents, new surgical methods, and targeted radiotherapy protocols have improved the survival rate and reduced the likelihood of an unfavorable course of the disease. Such patients may need to be admitted to an inpatient rehabilitation facility before, during, or after treatment. The results of various studies indicate that the participation of multidisciplinary specialists in the rehabilitation of oncological patients improves the functional results and quality of life of such patients [7]. Thus, D. Razavi, and N. Delvaux divide the stages of psychosocial care for patients and their families into five stages: prevention, early detection, recovery, support, and palliative care [8].

Medical rehabilitation in Russia is a complex of medical and psychological measures aimed at full or partial restoration of impaired organ or body system and/or compensation for lost functions of the affected ones. Among the physiological and medical indicators, the psychophysiological features of oncological patients can act as factors influencing the choice of a rehabilitation strategy, the timing of the beginning of the early rehabilitation period, its duration in general, and the predicted result of recovery.

World-wide studies reveal the data indicating the connection between the prognostic outcome of cancer, the effective response of the body to antitumor treatment, and the psychological characteristics of oncological patients [9], and examine the attitude to the disease, the interconnection of anxiety, coping strategies, and defense

mechanisms [10–12]. These mechanisms may also underlie rehabilitation processes, affecting the time of recovery of oncological patients after treatment and rehabilitation, as well as the duration of the period of remission.

The use of various methods of psychosocial rehabilitation can significantly reduce the anxiety of oncological patients at the stage of rehabilitation, improve self-confidence, and return to the previous (approximate) level of social role functioning, which can also lead to a return to professional activity after treatment [13]. Thus, the participation of oncological patients in psychological group training designed to address the emotional realm and mastering communication skills, increases the indicators of cognitive performance, changes the attitude to the consequences of cancer [14].

The objective of the study was to determine a list of psychological characteristics associated with the prognosis of prostate cancer outcome and rehabilitation potential in patients with cancer.

MATERIALS AND METHODS

In order to study the psychological markers of rehabilitation potential, the subjective and personal characteristics of the study participants were evaluated according to the following psychological methods:

1. Basic Beliefs Scale (World Assumptions Scale, R. Janoff-Bulman, adapted by M.A. Padun, A.V. Kotelnikova [15]). This questionnaire is based on the cognitive concept of a person's basic beliefs, including five subscales: "Benevolence of the surrounding world", "Justice", "Self-image", "Luck", "Beliefs of control". The questionnaire includes 37 items. Examinees need to express their agreement with each statement on a six-point scale, ranging from "Totally disagree" (1 point) to "Totally agree" (6 points). The main purpose of the method is clinical and psychological diagnostics of people who have experienced mental trauma and are presumably in a state of depression. The values of Cronbach's alpha coefficient of internal consistency for the subscales range from 0.62 to 0.79.

2. The method "Questionnaire of ways to cope" by R. Lazarus (adapted by T.L. Kryukova, E.V. Kuftyak, M.S. Zamyshlyaeva) [16]. The method is intended for determining the coping mechanisms (coping strategies) as ways to overcome difficulties in various areas of mental activity. It includes 50 statements for which it is necessary to choose one of four options: "never", "rarely", "sometimes" or "often". The structure of the questionnaire consists of eight scales, each of which is aimed at measuring the manifestation of coping behavior strategies: "Confrontational coping", "Distancing", "Self-control", "Seeking social support", "Taking responsibility", "Avoidance", "Planning to solve problems", "Positive revaluation". The values of Cronbach's alpha coefficient of internal consistency for the subscales range from 0.78 to 0.89.

3. Methodology of Subjective Control Level (E.F. Bazhin, E.A. Golynkina, L.M. Et-

kind) [17]. The methodology evaluates the degree of a person's readiness to take responsibility for what is happening to them in various spheres of their life. It consists of 44 questions, forming seven scales: the scale of general internality, the scale of internality in the field of achievements, the scale of internality in the field of failures, the scale of internality in the family relations, the scale of internality in the field of industrial relations, the scale of internality in the field of interpersonal relations, the scale of internality in relation to health and disease. The values of Cronbach's alpha coefficient of internal consistency for the subscales range from 0.74 to 0.86.

4. Test of vitality (S. Maddi, adapted by D.A. Leontiev, E.I. Rasskazova) is aimed at studying the factors contributing to successful coping with stress and reducing internal tension [18]. The full version of the questionnaire includes 45 questions related to the assessment of indicators on the scales of "Commitment", "Control", and "Risk-taking". Examinees need to express the measure of agreement with the statements. The values of Cronbach's alpha coefficient of internal consistency for the subscales range from 0.72 to 0.86.

5. Questionnaire SF-36 "Assessment of the quality of life" is a non-specific questionnaire for assessing the quality of life of patients, which is widely used in conducting quality of life studies in Europe and in the USA, Italy, France, and Australia [19]. The eight scales of the methodology are grouped into two indicators: "Physical component of health" and "Psychological component of health", a total of 36 items. The questionnaire contains the following sub-scales: "Physical functioning", "Role-functioning due to physical state", "Bodily pain", "General health", "Mental health", "Role-functioning due to emotional state", "Social functioning", "Vitality". The questionnaire is presented in several blocks, which use 5-point or dichotomous scales of response. The values of Cronbach's alpha coefficient of internal consistency for the subscales range from 0.76 to 0.84. Translation into Russian and interpretation of the methodology was carried out by the Institute of Clinical and Pharmacological Research, St. Petersburg.

The study involved men (n = 148) with a histologically confirmed diagnosis of malignant neoplasm of prostate gland. The sociological and statistical characteristics are presented in Table 1.

The study participants received a part of the radical course / full course of treatment for prostate cancer in accordance with the amount of therapy regulated by current Russian clinical guidelines, and went to the next stage of the treatment program or to an outpatient monitoring to control the disease. In the study group, 33 patients (22.2 %) showed stabilization of the process, progression was recorded in 36 patients (24.3 %), PSA-relapse (without other clinical signs) – in 32 (36.95 %), generalization was detected in 11 patients (7.4 %), the second cancer in 11 patients (7.4 %), remission – in 20 patients (13.5 %). Overall survival for one year in group was

recorded in 148 patients (100 %), two years – in 143 patients (96.6 %). The cause of death in 5 (3.3 %) patients was disease progression.

Table 1

Clinical characteristics of study participants (*n* = 148)

Characteristics	Abs Features. (%)
Histological structure of the tumor:	
G1	26 (17.39)
G2	109 (73.92)
G3	13 (8.77)
Assessment of cancer differentiation	
Gleason Score 7 (3+4)	109 (73.92)
Glisson Score 8 (4+4)	39 (26.08)
Age:	
under 60 years	19 (12.8)
61–70 years	66 (44.6)
71–80 years	57 (38.5)
over 81 years	6 (4.1)
The size of the tumor and its invasion into neighboring tissues and organs.	
T1	19 (13.04)
T2	99 (67.39)
T3	17 (10.88)
T4	13 (8.69)
Stages of the disease:	
early stages of the disease (stages 1–2)	95 (64.2)
bone lesion (stages 3–4)	53 (35.8)

The oncological patients (*n* = 148) were invited to participate in the study. The psychologist explained the goals and methods of the study, and received informed consent from the patients to participate. The survey of the patients was conducted after consultation with an oncologist and after confirming the course of the disease (remission, stabilization, generalization, relapse, progression).

The study participants were divided into groups according to the prognosis of the outcome of prostate cancer:

1.Group 1. Favorable course of the disease (stabilization, remission).

2.Group 2. Unfavorable course of the disease (generalization, relapse, progression, second cancer). In this group, subgroup 2A was singled out separately, where the fatal outcome was determined within 3–4 months after studying the subject and personal characteristics.

Statistical analysis: the significance level was set at 0.05. All statistical analyses were conducted using the IBM SPSS Statistics software version 26. Descriptive statistics and discriminant analysis were used.

All stages of the study comply with the legislation and regulatory documents of research organizations, as well as approved by the Bioethics Committee of the FSBEI HE (Federal State Budgetary Educational Institution of Higher Education) "National and Research "Tomsk State University" (Tomsk, Russia) (No. 5 dated February 11, 2021). Patients were informed about the goals and objectives and signed a written informed consent to conduct the study.

RESULTS AND DISCUSSION

The study participants' subjective and personal characteristics were studied: cognitive beliefs, coping strategies, quality of life

indicators, subjective control, personal helplessness/independence, and vitality. Tables 2–5 present the results of descriptive statistics (*M, SD*) of psychological characteristics in men with prostate cancer, as well as the reference values of diagnostic methods.

Table 2

Basic beliefs in men with prostate cancer

Basic beliefs	Mean values (standard deviation)			
	Group 1. Men with a favorable course of prostate cancer, *n* = 53	Group 2. Men with an unfavorable course of prostate cancer, *n* = 95	Group 2A. Men with fatal outcome of prostate cancer, *n* = 5	Normative reference values
Benevolence of the surrounding world, points	33.1 (6.4)	34.9 (5.6)	41.0 (4.3)	31.9 (5.1)
Justice, points	21.2 (4.3)	21.5 (4.2)	20.3 (0.5)	22.6 (3.6)
Self-image, points	26.2 (3.8)	26.5 (5.2)	24.0 (1.0)	25.2 (3.2)
Luck, points	29.2 (6.5)	30.8 (4.6)	29.3 (6.0)	27.3 (3.3)
Beliefs of control	25.1 (4.9)	26.7 (4.0)	28.0 (1.0)	25.9 (3.6)

Table 3

Coping strategies for men with prostate cancer

Coping strategies	Average values (standard deviation)			
	Group 1. Men with a favorable course of prostate cancer, *n* = 53	Group 2. Men with an unfavorable course of prostate cancer, *n* = 95	Group 2A. Men with fatal outcome of prostate cancer, *n* = 5	Normative reference values
Confrontational coping, points	8.6 (3)	8.2 (3.1)	10.00 (2.6)	8.9 (2.7)
Distancing, points	8.7 (3.5)	9.5 (3.1)	10.6 (1.5)	8.6 (3)
Self-control, points	12.6 (4.1)	11.8 (3.9)	14.0 (2.6)	13.6 (3)
Seeking social support, points	9.6 (3.9)	11.3 (5.4)	12.3 (2.5)	10.6 (3.1)
Taking responsibility, points	7.7 (2.3)	7.4 (2.6)	9.7 (2.5)	7.3 (2.1)
Avoidance, points	10.4 (3.7)	10.4 (4.2)	10.0 (2.0)	10.5 (3.5)
Planning to solve problems, points	12.1 (3.5)	11.6 (3.6)	13.3 (1.5)	12.7 (2.8)
Positive revaluation, points	1 12.0 (4.9)	11.0 (4.1)	15.0 (1.7)	12.3 (3.4)

Table 4

Average values of quality of life indicators in men with prostate cancer

Quality of life indicators	Average values			
	Group 1. Men with a favorable course of prostate cancer, *n* = 53	Group 2. Men with an unfavorable course of prostate cancer, *n* = 95	Group 2A. Men with fatal outcome of prostate cancer, *n* = 5	Normative reference values
Physical functioning (PF), points	65.6	65.2	63.3	77
Role-functioning due to physical state (RP), points	43.6	28.2	8.3	53.8
Bodily pain (BP), points	60.9	59.1	52.3	61.3
General Health (GH), points	49.2	47.4	36.6	56.5
Vitality (VT), points	60.1	51.2	33.3	55.1
Social functioning (SF), points	69.2	71.8	54.2	69.6
Role-functioning due to emotional state (RE), points	54.3	41.9	11.1	57.2
Mental Health (MH), points	65.9	60.7	38.7	58.8

Table 5

Indicators of subjective control in men with prostate cancer

Indicators of subjective control	Mean values/walls (standard deviation)		
	Group 1. Men with a favorable course of prostate cancer, *n* = 53	Group 2. Men with an unfavorable course of prostate cancer, *n* = 95	Group 2A. Men with fatal outcome of prostate cancer, *n* = 5
General internality, points/STEN scores	14.1 / 4 (6)	13.8 / 4 (6)	20.0 / 4 (8)
Internality in the field of achievements, points / STEN scores	4.2 / 5 (6)	4.6 / 5 (5)	2.7 / 5 (4)
Internality in the field of failures, points/ STEN scores	2.4 / 4 (7)	2.5 / 4 (5)	5.7 / 5 (7)
Internality in the field of family relations, points/ STEN scores	0.3 / 3 (5)	0.5 / 3 (5)	3.0 / 3 (8)
Internality in the field of industrial relations, points/ STEN scores	6.6 / 6 (6)	6.2 / 6 (5)	7.0 / 6 (5)
Internality in the field of interpersonal relations, points/ STEN scores	1.2/ 5 (3)	0.8/ 5 (3)	1.0/ 5 (2)
Internality in relation to health and disease, points/ STEN scores	0.5/ 3 (3)	–0.2/ 3 (1)	–2.0/ 2 (2)

Table 6

Vitality indicators for men with prostate cancer

Indicators	Mean values (standard deviation)			
	Group 1. Men with a favorable course of prostate cancer, $n = 53$	Group 2. Men with an unfavorable course of prostate cancer, $n = 95$	Group 2A. Men with fatal outcome of prostate cancer, $n = 5$	Normative reference values
Commitment, points	29.2 (11.5)	24.4 (12.2)	19.0 (16.8)	37.6 (8)
Control, points	23.9 (8.1)	24.5 (7.3)	27.0 (6)	29.1 (8.4)
Risk-taking, points	12.8 (6.9)	13.9 (7.9)	16.7 (5.1)	13.9 (4.3)
Outcome indicator of vitality, points	65.9 (20.7)	62.9 (18.9)	62.7 (18.6)	80.7 (18.5)

Average values of indicators of cognitive beliefs included in the worldview indicate that men with prostate cancer with an unfavorable prognosis of the outcome are characterized by beliefs in the benevolence of the surrounding world, its relative justice, belief in their own value and significance, their own luck and ability to control what is happening. Moreover, the participants of the study who subsequently died of prostate cancer were also confident in their luck, justice of the world, had a positive image of themselves, they firmly believed in the possibility of controlling what was happening and the benevolence of the surrounding world. The obtained data on the features of the worldview of men who subsequently recorded a fatal outcome are consistent with the previously obtained results on the selection of women with breast cancer [20].

The results of evaluation of coping strategies in study participants with different prognosis and outcome of prostate cancer indicate that the preferred coping strategies are “Self-control”, “Planning to solve problems” and “Positive revaluation”. Overcoming negative experiences of oncological patients was carried out by suppressing and restraining emotions (“Self-control”), analyzing the situation and options for solving the problem (“Planning for solving problems”), as well as by positively rethinking a difficult situation, considering it as a stimulus for personal development (“Positive revaluation”). However, the values of these coping strategies in respondents with a favorable and unfavorable prognoses of the outcome do not exceed the reference values of the questionnaire, whereas in respondents with a fatal outcome, they are significantly higher than the reference ($p < 0.001$).

In study participants with an unfavorable prognosis and fatal outcome of prostate cancer, the indicators of quality of life were reduced relative to normative reference values, with the exception of

"Social functioning" (SF) and "Mental Health" (MH). Reduced quality of life indicators are probably associated with the severity of cancer symptoms, yet cancer patients find the resources to feel active and experience positive emotions, which may also be related to the characteristics of coping behavior found in the study participants.

The indicators of the scales "Role-functioning due to the physical state" (RP) and "Role-functioning due to emotional state" (RE), which reflect the contribution of physical and emotional problems to role functioning of a person, were significantly reduced in the study participants with an unfavorable prognosis and fatal outcome of prostate cancer. These indicators of quality of life related to physical and emotional state, being indicators of the rehabilitation potential of an oncological patient, can be a point of application of the efforts of doctors in the process of complex rehabilitation, in particular, an ergotherapist and a psychologist [21].

Critically lower are all indicators of quality of life in study participants with a fatal outcome of the disease, which is due to severe symptoms of prostate cancer at stage 4 and with an unfavorable course.

According to the normative reference values of the questionnaire, when the indicator value is less than 5.5, the respondent is diagnosed with an external locus of subjective control. The results reveal that all participants in the study with prostate cancer have an external locus of control: men tend to explain the reasons for what is happening in their lives by external circumstances, other people, fate, luck or failure, while excluding their own contribution. However, internality is being diagnosed in the field of industrial relations. Men with prostate cancer with different prognosis and outcome recognize their own efforts and actions as the causes of success and failure related to their professional self-realization.

The obtained data on vitality in men with prostate cancer with different prognosis and outcome indicate its low rates, which reveals the unwillingness of men with prostate cancer to overcome life difficulties, control significant events, and get involved in life processes (due to externality). Speaking about individual indicators of vitality, it can be found that "Commitment" as involvement in the events of one's own life is higher in men with a favorable course of the disease than in men with an unfavorable prognosis and outcome. The "Risk-taking" indicator reflects a person's belief that life events contribute to the development and acquisition of new valuable experiences. The study participants with fatal outcome of prostate cancer demonstrated a high level of risk-taking compared to other indicators of vitality, which could be related to the life situation of the respondents, that is, the fight against a life-threatening disease.

The discriminant analysis was conducted in order to determine the discriminant variables, as well as to carry out the assessment of the role (contribution) of psychological characteristics in predicting the outcome.

In the course of discriminant analysis using a step-by-step method, a discriminant function was obtained, including: "Benevolence of the surrounding world" (λ = 0.828); "Distancing" (λ = 0.805); "Role-functioning due to emotional state" (λ = 0.780); "Social functioning" (λ = 0.782); "Beliefs of control" (λ = 0.785); "Commitment" (λ = 0.776); "Seeking social support" (λ = 0.770). The resulting discriminant function has a good predictive ability, as it explains 100 % of the variance (λ = 0.754; p = 0.001), 74.4 % of the initial grouped observations were classified correctly.

Thus, based on the data obtained, it can be suggested that a favorable prognosis for patients with prostate cancer may be related to their engagement in life events, active involvement in them, emotional investment, comprehension of the significance of the problem, partial independence from others, a slight restriction of role-functioning due to emotional state, optimal social functioning (social involvement) in combination with beliefs in the benevolence of the surrounding world and their ability to control events.

Furthermore, by evaluating the coefficients of the canonical discriminant function, we can say that the greatest contribution to the nature of the course of prostate cancer based on the psychological characteristics studied in this research are belief in the benevolence of the surrounding world (0.696), distancing (0.564), and social involvement (0.465). The least significant factor is seeking social support.

Thus, in the course of the study, a system of psychological predictors (the list) was obtained related to a favorable or unfavorable prognosis of the outcome of prostate cancer: basic beliefs – benevolence of the surrounding world, beliefs of control; coping behavior strategies – distancing, seeking social support; quality of life indicators – role-functioning due to emotional state, social functioning; an indicator of vitality – commitment. These psychological characteristics can help to determine the rehabilitation potential, being associated with the possibilities of recovery after antitumor treatment.

Conclusion

The basis of modern technologies for the rehabilitation of oncological patients is a biopsychosocial approach. The treatment and rehabilitation of an oncological patient also includes psychological support, since most patients experience fear, anxiety, distress, very often depression and other psychological issues [22]. This study presents an analysis of the psychological characteristics of men with prostate cancer with a different course of the disease, as well as the correlation of psychological characteristics

with the normative reference values. The study identified the list of psychological characteristics among those studied that are associated with a favorable course of cancer and rehabilitation potential: 1. Benevolence of the surrounding world; 2. Distancing; 3. Role-functioning due to emotional state; 4. Social functioning; 5. The beliefs of control; 6. Commitment; 7. Seeking social support, social activity.

The psychological variables obtained during the analysis can form the basis of psychological rehabilitation as a direction of rehabilitation in general. The psychological characteristics studied in this research related to the course of the disease may become psychotherapeutic targets for psychologists from an interdisciplinary team whose goal is to support oncological patients, improve their quality of life, and enhance the effectiveness of therapy for this patient group. The perspective of the study is to provide a psychological intervention that can help optimize the psychological characteristics of patients diagnosed with prostate cancer.

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Funding. The study was supported by a grant from the Russian Science Foundation № 21-18-00434, https://rscf.ru/project/21-18-00434.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

Ponomareva I.V. – research design, analysis of the obtained data, writing the test.

Kuznetsova A.I. – collection and processing of empirical data, writing the test.

Vazhenin A.V. – concept and design of the study.

Tsiring D.A. – concept and design of the study.

Pakhomova Ya.N. – collection and processing of materials, analysis of the obtained data, writing the text.

Mironchenko M.N. – collection and processing of empirical data, analysis of the obtained data.

Received: 27/11/2023
Revised version received: 12/05/2023
Accepted: 03/06/2024

Please cite this article in English as: Ponomareva I.V., Kuznetsova A.I., Vazhenin A.V., Tsiring D.A., Pakhomova Ya.N., Mironchenko M.N. Rehabilitation potential in patients with prostate cancer: psychological aspect. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 19-32. DOI: 10.17816/pmj41219-32

Scientific Article
UDC 616-006, 616.37-006.6
DOI: 10.17816/pmj41233-41

ANALYSIS OF THE OCCURRENCE OF GERMLINE MUTATIONS BRCA1\2, PALB2, CHEK2, NBN IN PATIENTS WITH PANCREATIC MALIGNANCIES. SINGLE-CENTER COHORT NON-RANDOMIZED RETROSPECTIVE STUDY

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АНАЛИЗ ВСТРЕЧАЕМОСТИ ГЕРМИНАЛЬНЫХ МУТАЦИЙ BRCA1\2, PALB2, CHEK2, NBN У ПАЦИЕНТОВ СО ЗЛОКАЧЕСТВЕННЫМИ НОВООБРАЗОВАНИЯМИ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ: ОДНОЦЕНТРОВОЕ КОГОРТНОЕ НЕРАНДОМИЗИРОВАННОЕ РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

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Objective. To analyze the frequency of carriage of BRCA1\2, PALB2, CHEK2, NBN mutations in patients with malignant neoplasms of pancreas.
Materials and methods. The single-center cohort non-randomized retrospective study is based on the data of 82 patients who were examined and treated in Russian Research Center of Radiology and Surgical Technologies named after academician A.M. Granov from 2020 to 2022. Patients with confirmed ductal adenocarcinoma of pancreas were included into the study group. Screening of mutations in exons 2,10, 18, 19 of BRCA1 gene and exon 11 of BRCA2 gene was performed in these patients. In addition, oncological family histories were studied.
Results. Analysis of medical documentation data showed that 18 (22 %) patients with pancreatic cancer had a hereditary oncological history. In this cohort of patients, 5 (28 %) had relatives with pancreatic cancer, 9 (50 %) had a family history of ovarian cancer, 2 (11 %) female relatives of patients in the study group were diagnosed with breast cancer before the age of 50, also 2 (11 %) patients had a history of more than 2 relatives who suffered from breast cancer and / or prostate cancer. When evaluating the results of revealing the mutations in the entire study group (82 patients), BRCA1 (c.5266dupC) was revealed in 8 patients (9.7 %), PALB-2 (c.1592delT) – in 2 patients (2.4 %), mutations CHEK2, NBN and BRCA2 were not diagnosed in any patient. 5 (6 %) patients who were BRCA1 mutation carriers and one patient with an established PALB2 mutation, according to the analysis of case histories, had no oncological history. None of the patients in the study group was a carrier of the BRCA2, CHEK2 and NBN mutations.
Conclusions. Some patients with pancreatic cancer are carriers of germline mutations. Considering our data on the trend of association between germline mutations and pancreatic cancer, we can make an assumption about the prospect of using this indicator as one of the markers for early detection of pancreatic cancer not only in patients with hereditary risk factors for neoplasia, but also in patients without cancer anamnesis. To obtain the results, further observation of patients in the study group and randomized multicenter studies are required.
Keywords. Pancreatic cancer, germline mutations, BRCA1, BRCA2, PALB2.

Цель. Проведение анализа частоты носительства мутаций BRCA1\2, PALB2, CHEK2, NBN у пациентов со злокачественными новообразованиями поджелудочной железы (ЗНО ПЖ).
Материалы и методы. В одноцентровое когортное нерандомизированное ретроспективное исследование включены данные 82 пациентов, прошедших обследование и лечение в ФГБУ РНЦРХТ им акад. А.М. Гранова в период с 2020 по 2022 г. В группу исследования включены пациенты с морфологически подтвержденным диагнозом протоковой аденокарциномы поджелудочной железы. У этих больных проводили скрининг мутаций в экзонах 2, 10, 18, 19 гена BRCA1 и в ключевом регионе 11-го экзона гена BRCA2. Дополнительно проводили изучение семейного онкологического анамнеза.
Результаты. Анализ данных медицинской документации установил, что 18 (22 %) больных ЗНО ПЖ имели наследственный онкологический анамнез. В данной когорте 5 (28 %) человек сообщили о случаях ЗНО ПЖ у родственников, 9 (50 %) имели семейный анамнез рака яичников, у 2 (11 %) родственниц пациентов группы исследования диагностирован рак молочной железы до возраста 50 лет, также у 2 (11 %) пациентов в анамнезе было более 2 родственников, которые страдали раком молочной железы и/или раком простаты. При оценке результатов определения мутаций во всей исследуемой группе (82 человека) BRCA1 (c.5266dupC) выявлена у 8 пациентов (9,7 %), PALB-2 (c.1592delT) – у 2 (2,4 %), мутаций CHEK2, NBN и BRCA2 – не диагностировано ни у одного пациента; 5 (6 %) носителей BRCA1 мутации и один пациент с установленной мутацией PALB2, по данным анализа историй болезни, не имели онкологического анамнеза. Ни один из пациентов группы исследования не являлся носителем BRCA2, CHEK2 и NBN мутации.
Выводы. Некоторые пациенты, страдающие ЗНО ПЖ, являются носителями герминальных мутаций. Учитывая полученные нами данные о тенденции связи герминальных мутаций и рака поджелудочной железы, можно сделать предположение о перспективе использования данного показателя в качестве одного из маркеров раннего выявления рака поджелудочной железы не только у больных с наследственными факторами риска возникновения данной неоплазии, но и у пациентов без онкологического анамнеза. Для получения дальнейших результатов требуется продолжение набора пациентов в группу исследования и проведение рандомизированных мультицентровых исследований.
Ключевые слова. Злокачественные новообразования поджелудочной железы, герминальные мутации, BRCA1, BRCA2, PALB2.

INTRODUCTION

According to the World Cancer Research Fund, malignant neoplasms of pancreas occupy a leading position among all oncological diseases of the gastrointestinal tract in terms of late detection and mortality. Unfavourable medical and statistical indicators of pancreatic cancer are associated with late treatment of patients, as well as with tumour resistance to existing chemotherapy regimens. Due to the absence of screening and detection programs for patients with pancreatic cancer, the disease is represented by a locally advanced or metastatic stage in more than 80 % of cases at the time of primary diagnosis, which significantly worsens the prognosis of the disease and the results of treatment [1; 2]. Given the lack of recognized biomarkers for early detection of pancreatic cancer, as well as the difficulties of instrumental diagnosis of this pathology at early, preclinical stages, the search for "markers" for detecting pancreatic cancer is an urgent problem in modern clinical oncology [3]. One of the possible methods for early detection of pancreatic cancer is genetic testing in risk groups and patients with a family history of pancreatic cancer [4]. During normal cell functioning, genome stability is maintained by a system for recognizing DNA sequence defects by ATM and ATR kinases, CHEK2 and BRCA1 signal conversion molecules, and BRCA2 and RAD51 repair initiation effectors. The system also contains the molecules that coordinate the interaction of recognition and repair, such as PALB2 and BRIP1. It should be noted that it is BRCA2 that plays a more specific role in DNA repair, regulating the RAD51 activity required for homologous recombination. According to a number of authors, it is disorders in this system that play a fundamental role in the development of pancreatic cancer [5]. A multicenter IMPACT study conducted by a group of authors from the USA indicated that out of 76 patients suffering from common forms of prostate cancer 21.5 % had germinal mutations [6]. In general, there is evidence in the literature that the presence of BRCA gene mutations increases the risk of pancreatic cancer, but the effect of these mutations on the clinical course of the disease is insufficiently studied. The cohort studies have shown that patients with pancreatic cancer who carry germinal mutations BRCA1, BRCA2, PALB2, CDKN2A, and ATM are diagnosed with the disease earlier than patients without mutations [7; 8]. However, a study conducted by C. Ferrone et al. in a population of Ashkenazi patients with pancreatic cancer did not reveal significant differences between the presence of BRCA mutations and any clinical and pathological signs of the disease, including the moment of manifestation of pancreatic cancer [9]. The prognostic role of BRCA mutations in pancreatic cancer has not been definitively determined. Study by T. Golan et al., which included patients with pancreatic cancer with different BRCA mutation statuses, revealed that the median overall survival of patients receiving therapy in the presence of BRCA mutations was 14 months, and for patients without established germinal mutations – 12 months. It should be noted that at the time

of publication, the median overall survival in patients with early-stage pancreatic cancer was not achieved at all, since 52 % of patients had been alive for 60 months from the start of the study [10].

The data obtained by the authors indicate that patients with pancreatic cancer and detected BRCA mutations may have a significantly better prognosis than the general population of patients with pancreatic cancer. More recent case-control studies conducted by Blair et al. showed that the overall survival and relapse-free period after surgery in patients with pancreatic cancer and BRCA1 and BRCA2 mutations was significantly lower compared to the control group without mutations. Another case-control study comparing patients with early-stage pancreatic cancer with a BRCA mutation who underwent surgical resection and a control group with BRCA-wild type did not reveal statistically significant differences in the median overall survival in the groups, thus, the authors concluded that BRCA mutations did not have prognostic significance in the early stages of pancreatic cancer [11]. Most of the reported cases of pancreatic cancer are considered sporadic, however, approximately 5 to 10 % are related to a family history of the disease, which is defined as presence of two or more first-degree relatives or three or more relatives of any degree with a diagnosis of pancreatic cancer [12]. Nevertheless, the research in different populations, including patients with pancreatic cancer, confirmed the absence of a clear connection between the presence of BRCA mutations and family history [13; 14]. Taken together, obtained literary data convincingly confirm the extension of indications for genetic testing for patients at risk of pancreatic cancer without a family history. Thus, a clinical study of BRCA1\2 mutations can be of great practical importance in detecting and predicting pancreatic cancer, including in patients without a family history of malignant neoplasms and hereditary syndromes.

The objective of the study: to analyze the incidence rate of BRCA1\2, PALB2, CHEK2, and NBN germinal mutations in patients with malignant neoplasms of pancreas.

MATERIALS AND METHODS

The single-center cohort non-randomized retrospective study is based on the data of 82 patients who were examined and treated in Russian Research Center of Radiology and Surgical Technologies named after academician A.M. Granov from 2020 to 2022. Analysis was performed by new generation sequencing by screening in BRCA1 (538insC, 415delA, 185delAG, T300G, c. 2080insA, c. 208delA, 3875delGTCT, 3819delGTAA, c. 5251C>T, c. 4675G<A, c. 5177 5180delGAAA), BRCA2 (6174delT, c. 3749dupA, c. 961 962ins AA), CHEK2 (c.1100delC, c.444+1G>A, c.839 897del, c.470T>), PLAB2 (c. 1592delT), NBN (657del15). Screening of mutations in exons 2, 10, 18, and 19 of the BRCA1 gene and in the key region of exon 11 of the BRCA 2 gene was performed. Additionally, family history of cancer was investigated. The NCCN 2023 criteria were used as genetic risk factors for pancreatic cancer.

RESULTS AND DISCUSSION

In the study group, the age of patients ranged from 51 to 79 years; the median age was 64.3 years. The number of men – 46 (57 %), women – 36 (43 %) (Table).

Analysis of medical records showed that 18 (22 %) patients had a hereditary history of cancer. Herewith, 5 (28 %) patients reported cases of pancreatic cancer in relatives, 9 (50 %) patients had a family history of ovarian cancer, 2 (11 %) relatives of patients in the study group were diagnosed with breast cancer before the age of 50, while 2 (11 %) patients had a history of more than 2 relatives who suffered from breast cancer and/or prostate cancer.

It should be noted that none of the patients in the study group identified themselves with the Ashkenazi ethnic group. In the group of patients with a history of pancreatic cancer, germinal mutations were detected in 3 patients (two patients were carriers of the BRCA1 mutation (p. 5266dupC), another patient had the PALB2 mutation (p.1592delT)). The mother of one BRCA1 carrier was diagnosed with breast cancer before the age of 50, and the father of the second BRCA1 carrier had pancreatic cancer. Notably, the latter patient's maternal grandmother suffered from breast cancer, and his paternal cousin died of colon cancer. The CECK2 mutation was diagnosed in a patient whose grandmother and grandfather suffered from breast cancer and prostate cancer, respectively.

5 (6 %) patients who carried the BRCA1 mutation and one patient with the determined PALB 2 mutation did not have a history of cancer according to the analysis of medical records. It should be mentioned that one of the carriers of the BRCA1 mutation was diagnosed with advanced prostate cancer during the examination. None of the patients in the study group were carriers of the BRCA2, CHEK2, and NBN mutations.

Most of the reported cases of pancreatic cancer are considered sporadic, however, approximately 5 to 10 % are related to a family history of the disease, while the risk of developing pancreatic cancer during life in the presence of this disease in the family history increases 2.3–3.2 times, depending on the number of sick relatives [12]. In our study, 22 % of patients had a hereditary history of cancer. According to the analysis, most often – in 9 (50 %) and 5 (28 %) patients – blood kin suffered from pancreatic cancer and ovarian cancer, respectively. In the study of M. Cote et al., which included

Distribution of patients with a family history of cancer by hereditary risk factor (NCCN criteria, 2023)

Hereditary factor	Breast cancer in at least one relative under the age of 50	Pancreatic cancer in a first-degree relative at any age	Ovarian cancer in a first-degree relative at any age	Breast and/or prostate cancer in more than two relatives at any age
Number of patients, abs. (%)	2 (11)	5 (28)	9 (50)	2 (11)

more than 350 patients with pancreatic cancer, relatives most often suffered from pancreatic cancer and ovarian cancer as well [16]. According to the authors, the connection between ovarian cancer and prostate cancer is based on the presence of BRCA2 mutations. In the study of M. Roberts et al. It was found that in 14 % of the population of patients with prostate cancer, mutations are detected in the genes responsible for BRCA 2 DNA repair [12]. However, in our study, no BRCA2-mutation was detected in any patient. The obtained data can probably be explained by the fact that BRCA2 mutations are relatively rare in Russia, and their spectrum is not limited to repeated injuries [17].

The literature describes hereditary syndromes and diseases that are associated with an increased risk of developing pancreatic ductal adenocarcinoma (PDAC), including: familial atypical multiple mole melanoma syndrome (FAMMM-syndrome), Peutz–Jeghers syndrome, and Lynch syndrome [18]. In our study, the above-mentioned hereditary syndromes were not registered in any patient. This may be due to the fact that these syndromes are relatively rare in the population – less than 5 % [19].

In recent times, recommendations for genetic testing of inherited pancreatic cancer have been increasingly criticized by various researchers, as annually updated data appear indicating that existing screening algorithms based on family history are ineffective, which leads to late detection of these neoplasms. In 2007, a study of patients with BRCA1/2 mutations conducted by a group of authors from Norway revealed that 50 % of patients with BRCA germ line mutations do not have a family history of cancer associated with BRCA gene mutations [13; 20]. In our study, more than a half of patients with determined germinal mutations did not have a family history of cancer.

Special attention should be paid to the statistical data of the Ashkenazi ethnic group, since in this group the occurrence of germinal mutations, especially BRCA2 (6174delT), is extremely high, and therefore should be considered separately [20]. In our study, none of the patients associated themselves with this ethnic group. It should be noted that there are some references in the literature about the results of direct genetic testing, according to which 20 % of carriers of Ashkenazi genes do not identify themselves as descendants of this ethnic group and, therefore, may potentially be excluded from the screening criteria of existing programs that include Ashkenazi origin as one of the fundamental risk factor for developing hereditary forms of cancer, prostate cancer in particular. Moreover, in this study, the authors found that out of 393 carriers of BRCA1\2 gene mutations with available family history of cancer, 44 % did not have a family history of BRCA-related cancer [21].

Conclusion

Thus, a number of patients suffering from pancreatic cancer are carriers of germinal mutations. If we take into account our data on the trending association between germinal mutations and pancreatic cancer, we can make an assumption about the prospects of using this indicator as one of the markers for detecting pancreatic cancer in patients at risk. Consider-

ing the fact that only a third of patients with pancreatic cancer had a history of cancer, it is advisable to determine germinal mutations for early detection of pancreatic neoplasia in patients without a history of cancer as well. It seems promising to identify "risk groups" for the development of pancreatic cancer, based not only on data on hereditary risks of pancreatic cancer, but followed by an analysis of germinal mutations as one of the factors for the development of pancreatic cancer. Our study is characterized by a small sample of patients, which certainly may limit the obtained results. Continuing to recruit patients to the study group, as well as conducting multicenter, randomized prospective studies, will help to obtain further results for determining the place of germinal mutations in the diagnosis of pancreatic cancer in patients at risk of developing this type of neoplasia.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

Moiseenko V.E. – information collection, statistical data processing, interpretation of work results, writing the text.

Kardanova I.G. – data processing, writing the article text, preparing the article for publication.

Pavlovsky A.V. – writing the text and critical review of its content.

Avanesyan G.R. – statistical data processing, information collection.

Granov D.A. – a significant contribution to the concept and design of the work, general guidelines for writing the article, editing the article.

Received: 11/13/2023
Revised version received: 03/21/2023
Accepted: 03/25/2024

Please cite this article in English as: Moiseenko V.E., Kardanova I.G., Pavlovsky A.V., Avanesyan G.R., Granov D.A. Analysis of the occurrence of germline mutations BRCA1\2, PALB2, CHEK2, NBN in patients with pancreatic malignancies. single-center cohort non-randomized retrospective study. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 33-41. DOI: 10.17816/pmj41233-41

LITERATURE REVIEW

Scientific Review
UDC 616.895.8-02-092
DOI: 10.17816/pmj41242-51

CURRENT UNDERSTANDING OF THE ETIOLOGY AND PATHOGENESIS OF SCHIZOPHRENIA

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СОВРЕМЕННОЕ ПРЕДСТАВЛЕНИЕ ОБ ЭТИОЛОГИИ И ПАТОГЕНЕЗЕ ШИЗОФРЕНИИ

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The current literature data on the etiology and pathogenesis of schizophrenia were analyzed. The research method is the analysis of scientific papers on this problem over the past 5 years, presented in the databases of eLibrary, National Library of Medicine and electronic versions of the journals “World Psychiatry Journal”, “The Lancet Psychiatry”, “Schizophrenia Bulletin” and others. Genetic, neurotransmitter, psycho-traumatic,

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sociocultural and other theories of the origin and development of schizophrenia are analyzed in the review. Schizophrenia is a disease difficult to verify and genetically determined. According to modern theories, the occurrence of schizophrenia and the appearance of symptoms can be influenced by metabolic disorders of neurotransmitters, psycho-traumatic factors, socio-cultural aspects of human life, while the anatomical subcortical structures of the brain are damaged.
Keywords. Schizophrenia, psychopathology, etiology of schizophrenia, pathogenesis of schizophrenia, mental illness, mental trauma, genetics, serotonin, dopamine.

Проанализированы современные литературные данные о этиологии и патогенезе шизофрении. Методом исследования является анализ научных работ по данной проблеме за последние 5 лет, представленных в базах eLibrary, National Library of Medicine и электронных версиях журналов World Psychiatry Journal, The Lancet Psychiatry, Schizophrenia Bulletin и других. В обзоре проанализированы генетические, нейромедиаторные, психотравмирующие, социокультурные и другие теории возникновения и развития шизофрении. Шизофрения – трудно верифицируемое заболевание, оно является генетически обусловленным. Согласно современным теориям, на возникновение шизофрении и появление симптомов могут влиять нарушения метаболизма нейромедиаторов, психотравмирующие факторы, социокультурные аспекты жизнедеятельности человека, при этом происходит повреждение анатомических подкорковых структур головного мозга.
Ключевые слова. Шизофрения, психопатология, этиология шизофрении, патогенез шизофрении, психические болезни, психическая травма, генетика, серотонин, дофамин.

INTRODUCTION

Schizophrenia is a mental illness in which a person exhibits various positive (productive) symptoms, including hallucinations (seeing or hearing things that are not really there), delusional and catatonic states, mood changes, as well as negative symptoms such as apathy (lack of interest or motivation), problems with social adaptation. Schizophrenia can also cause disturbances in behavior and thought processes, problems with memory, attention and thinking[1].

The types of schizophrenia according to the ICD-10 classification include nine forms:

1) paranoid schizophrenia (F20.0);
2) hebephrenic schizophrenia (F20.1);
3) catatonic schizophrenia (F20.2);
4) undifferentiated schizophrenia (F20.3);
5) post-schizophrenic depression (F20.4);
6) residual schizophrenia (F20.5);
7) simple schizophrenia (F20.6);
8) another type of schizophrenia (F20.8);
9) schizophrenia unspecified (F20.9)[2].

Despite the fact that differential diagnostics of various forms of schizophrenia is difficult, it is possible to verify the form of the disease by collecting anamnesis, complaints and conducting a psychiatric interview taking into account the patient's mental status data. However, the etiology and pathogenesis are unclear, which complicates not only understanding the essence of

[1] Alfimov P.V., Erichev A.N., Lutova N.B., Maslenikov N.V., Mosolov S.N., Papsuev O.O., Tsukarzi E.E., Shmukler A.B. Clinical recommendations, Russian Federation 2021. Schizophrenia in adults. Russian Society of Psychiatrists, 2021; 119, available at: https://psychiatr.ru/download/4244?view=1&name=КР_+Шизофрения+25-11.pdf.

[2] ICD-10. International Classification of Diseases, 10th revision. Mental and behavioral disorders (F00–F99). Schizophrenia, schizotypal states and delusional disorders (F20–F29). version 2019, available at: https://mkb-10.com/index.php?pid=4160.

the disease causes, but also the possibility of etiotropic and pathogenetic treatment.

The objective of the study is to create a literature review to summarize information on current issues in the etiology and pathogenesis of schizophrenia over the past 5 years.

ETIOLOGY OF SCHIZOPHRENIA. GENETIC BACKGROUND

About a thousand genes and more than 100 loci have been identified that contribute to the development of schizophrenia by triggering pathophysiological mechanisms, but each of them in isolation has little effect on the risk of schizophrenia. Among them, there are no genes that absolutely determine the disease. This creates pronounced genetic heterogeneity of the disease [1].

Chromosomal aberrations (genomic aneuploidy and mosaic autosomal aneuploidy) and point mutations in the form of nucleotide substitution and copy number variations (duplications, deletions, insertions, inversions) have been identified. Genetically determined pathogenetic mechanisms manifest themselves under the influence of provoking exogenous factors. In some cases, sporadic schizophrenia is not supported by heredity. Mutations in the genes 1q21.1 del/dup, 3q29 del, 7q11.23 dup, 15q11.2 dup, 15q13.3 del/dup, 16p13.11 dup, 16p11.2 del/dup, 17q12 del, 22q11.2 del/dup are more common in people with schizophrenia than in other people without this disease [2; 3]. At the same time, these genes also encode other mental disorders, so they cannot be called obvious determinants of schizophrenia. An increased risk of developing schizophrenia is associated with the PLXNA2 gene in the rs752016 locus, which controls brain semaphorins. They, in turn, are involved in controlling the process of axon formation, modulate plasticity and are responsible for neuronal regeneration [4]. Of particular interest is the ANK3 gene on chromosome 10, which encodes the protein ankyrin 3. This protein coordinates the work of the axon and the maintenance of the action potential. In people with schizophrenia, its expression is reduced [5].

It has been established that changes in the DRD2 gene are associated with problems in the dopamine system, and in GRIN2B it affects the work of the glutamatergic system [6; 7].

The role of the C4 gene in the etiology of schizophrenia was clarified based on the correlation of haplotype and variability. It turned out that the risk is higher, the more copies of the gene in the genome, "long" copies with HERV-K (a mobile genetic element of a retrovirus) and copies of the C4A isotype [8].

MENTAL AND SOCIO-CULTURAL ASPECTS OF THE ETIOLOGY OF SCHIZOPHRENIA

According to the psychodynamic theory of the schizophrenia development, the etiology of this mental illness is directly related either to the stage of an unformed ego and an attempt to restore it (according to Z.S. Freud), or to overprotection and rejec-

tion of the child (according to F. Fromm-Reichmann) [9].

The behaviorist theory of the origin of schizophrenia emphasizes learning by trial and error, reinforcement of the stimulus response. Bizarre reactions attract the attention of others or bring other types of reinforcement, thus increasing the likelihood that a person will resort to them again and again.

According to the cognitive theory, people with schizophrenia try to understand their strange sensations. The presence of voices, images and other hallucinations begins to frighten them. When they tell their friends and family about this, they are often not believed. The patients themselves believe that something is being hidden from them. This can lead to the development of delusions of persecution. The cognitive theory of schizophrenia is considered one of the most convincing.

Family problems play an important role in the development of mental illnesses, including schizophrenia. Genetic predisposition can cause schizophrenia only in combination with severe emotional shocks, pathological amplifications and stress in the family or in the social life of the individual. When schizophrenia has already developed, social prejudices and problems in the family can worsen the situation or maintain symptoms [10].

Modern psychological researchers are paying more and more attention to the role of the family. It is believed that it is the violation of communication, both verbal and non-verbal, abuse, domestic violence, gaslighting, bullying that can influence the formation of erroneous views on their behavior in a growing child, which leads to the transformation of behavioral attitudes during the school period. When the child is again subjected to "family" rejection, the initially idiopathic symptoms are consolidated and transformed into truly organic symptoms based on dystrophy of the nervous structures of the peripheral nervous system and the brain, as well as dysfunction of transmitter systems [11].

Recent studies confirm that family factors play an important role in the development of mental health problems, including schizophrenia. Childhood trauma, abuse, and neglect may influence the onset of this disorder. For example, up to 65 % of people with schizophrenia report physical or sexual abuse in childhood. However, such abuse may also be associated with anxiety disorders and fears. It follows that the family factor of abuse, especially sexual abuse, must be compared with gender, age, stress factors, and genetic predisposition [12].

NEUROTRANSMITTER THEORIES

The dopamine theory considers disturbances in the regulation of dopamine synthesis and, as a consequence, the presence of cognitive impairments, which are the substrate for the development of the schizophrenia symptom complex. Scientists have proven that blocking D2 receptors with neuroleptics suppresses the development of positive symptoms of schizophrenia [13].

Although the dopamine theory is the most reliable at the moment, it, like the genetic theory, is subject to criticism on various points. In particular, a number of studies refute the mediation between a decrease in dopamine secretion, its content in the striatum and the appearance of positive schizophrenic symptoms in the form of dysfunction of the cognitive reactions intermediates: attention, thinking, memory, etc. [14].

The pineal gland hormone, melatonin, has an insignificant effect on the development of schizophrenia symptoms, which is confirmed by some studies with melatonin as a marker and therapeutic agent. Authors who have studied the effects of melatonin on schizophrenia report conflicting results. Melatonin levels in the blood of patients with schizophrenia may be high, low, or unchanged. Melatonin is most often used therapeutically to improve sleep and reduce tardive dyskinesia [15].

Melatonin has a wide range of effects in the tissues of our body. In humans, it controls circadian rhythms, acts as a hormone, neuromodulator, cytokine, and mediator of biological responses. It affects the functioning of the brain, immune system, gastrointestinal tract, heart, kidneys, bones, and endocrine system. Significantly, melatonin can also help slow down aging and has a beneficial effect on cancer cells [16].

NEURODEGENERATIVE THEORY

This theory considers the etiology of schizophrenia in terms of pathological changes in the brain, revealed by MRI and CT. In the absence of changes in the neurotransmitter component, in schizophrenia one can observe the expansion of certain internal cavities of the brain (ventricles), a decrease in the size of some areas of the brain (frontal and temporal lobes), changes in the structure of the basal ganglia and hippocampus, and sometimes also a decrease in the volume of the cerebellum. This proves that schizophrenia is an organic disease with damage to the structures of the brain [17].

VIRAL THEORY

Some studies show that the RNA level of some viruses, such as HIV, herpes, and Epstein-Barr virus, may be associated with schizophrenia. Studying the relationship between HIV infection and mental disorders helps us understand the causes and mechanisms of schizophrenia. There is also an idea about a possible connection between a distorted immune response to Epstein-Barr virus and type W retrovirus (HERV-W) and the development of schizophrenia [17].

IMMUNOLOGICAL THEORY

The immunological theory links the presence of schizophrenia in patients with an increase in the level of interleukins, namely IL-2 and IL-10. A correlation has been found between the depression of T-helpers and the formation of autoimmune reactions that contribute to the development of schizophrenia. At this stage, the increase in the permeability of the blood-brain barrier in this disease is being actively studied [18; 19].

HORMONAL THEORY

The concept of neurohumoral shifts underlies the hormonal theory. There is a hypothesis that changes in hormonal levels (reduced levels of sex hormones – estrogen and testosterone) trigger processes that lead to the development of schizophrenia. The relationship between neurotransmitter systems and hormones of the gonadal-pituitary hypothalamic axis, including estrogen, in schizophrenia has been proven. Estrogens have a neuroprotective effect, are able to modulate dopaminergic and other mediator systems involved in the pathogenesis of schizophrenia, and the estrogen-protective hypothesis, according to a number of authors, is valid for both women and men [20].

THEORY OF CORTICAL DISINTEGRATION

This theory is based on the presence of cortical atrophic disorders in patients with schizophrenia, accompanied by weakening or absence of gamma waves on the EEG, as well as changes in the P300 wave [21].

LEADING PATHOPHYSIOLOGICAL MECHANISMS OF SCHIZOPHRENIA

Modern research indicates that genetic predisposition plays a major role in the development of this disease. Various abnormalities associated with schizophrenia are found in genes that determine a variety of biological processes: proliferation and differentiation of nerve cells, their metabolism and functioning, as well as in genes involved in inflammatory, dystrophic, and autoaggressive processes. Thus, schizophrenia is a complex genetic disease caused by dysfunction of the dopaminergic, serotonergic, and glutamatergic systems. Schizophrenia can manifest itself in various situations, such as mental trauma and stress, with disruption of neurotransmitter metabolism.

According to the dopamine theory of schizophrenia, disruption of the regulation of dopaminergic neuron activity and changes in dopamine concentration in certain areas of the brain can lead to hallucinations and delusional thoughts. This is confirmed by the results of studies conducted not only with schizophrenia patients, but also with people suffering from alcohol or amphetamine psychosis [14].

There is an assumption that the glutamatergic and GABAergic systems may play a role in the development of schizophrenia. According to this hypothesis, problems with the NMDA receptor (a signaling protein) can disrupt the transmission of signals between cells, which leads to the appearance of schizophrenia symptoms. This can also increase dopamine activity in the brain. An increase in the amount of dopamine can aggravate the manifestations of schizophrenia. As a result of the unstable operation of these brain systems, problems with the control of excitability arise, which can lead to degeneration of nervous tissue and worsening of schizophrenia symptoms [21].

According to the theory of the influence of the situation in the family, contrib-

uting to the manifestation of schizophrenia, it is worth highlighting two pathogenetic mother's role models: a) mother is an imperious paranoid personality; b) mother is an anxious "mother hen".

In the first case, the mother's personality encourages the child to be independent, strong and overcome difficulties. But these ideas about the mother and her prohibitions remain active in difficult situations, preventing independence. As a result, an adult can react regressively and return to helpless behavior from childhood – this is an unhelpful form of adaptation.

In the second case, when the mother is a sensitive personality type with certain psychological traits, she raises the child in such a way that he is a hypochondriac, uninitiative and dependent. When the child asks for help, the mother tells him: "Don't complain, don't cry, don't pay attention, figure it out yourself!" As a result, an unhelpful situation is formed, where the mother controls everything, and the child ignores his needs, which can lead to conflicts, isolation and problems in communicating with other people [11; 12].

According to the "stress diathesis", people with schizoid personality traits can react to stress more strongly and for a longer time. When they are exposed to prolonged emotional stress, it can activate a biological factor associated with disrupted signaling in the brain. As a result, symptoms of hallucinations and delusions may appear [12].

Scientific research is actively searching for the role of astroglia in the development of schizophrenia. It has been proven that this disease is characterized by a decrease in the activity of auxiliary brain cells. Astroglia stops multiplying, microglia decrease in size, and oligodendroglia begin to reverse development. When nerve cells are destroyed, the body does not start the recovery process, which is often the case with other nervous diseases [22; 23].

In people suffering from schizophrenia, changes and death of cells responsible for the production of myelin occur. This makes communication between nerve cells less effective. Clinically, this is manifested by apathy, rapid fatigue, sleep disturbances and impaired social interaction. Myelination disorders lead to problems in synchronizing brain activity and a decrease in connections between its different areas. Significantly, damage to the myelin sheaths can be present even before the manifestation of the disease [17].

Immunogenetic factors are of particular importance in the development of schizophrenia, these factors are associated with certain genes that control the immune response. These are the C4A and C4B genes, which affect the number of connections between nerve cells in the brain, especially in childhood and adolescence. Some studies have also shown an increase in the levels of certain substances in the blood and cerebrospinal fluid, such as IL-1, IL-2, IL-6 and TNF-α. One cannot ignore the fact that there is a change in the number of T- and B-lymphocytes, as well as associated autoimmune disorders, which are considered the main mechanism for the development of schizophrenia according to the immunological theory of the disease. Data

on the correlation of leukocyte elastase with the appearance of negative symptoms of this disease indicate a significant role of immune pathology in the pathogenesis of schizophrenia [18; 19].

An important aspect of the pathogenesis of schizophrenia is the disruption of metacognitive processes (knowledge, experience, goals, strategy), which can lead to a breakdown in perception, problems in collecting information, and a sense of loss of connection with oneself and others. This can be an important factor in the development of schizophrenia, when patients feel a loss of their freedom and integrity. In some cases, patients are more concerned about the loss of meaning in their own identity than with psychotic symptoms [24].

In people with a genetic predisposition to schizophrenia, certain triggers, such as psychological trauma, stress, or social pressure, are required for the development of this disease [9].

Psychological trauma can greatly influence the development of schizophrenia in both men and women. For example, adverse experiences in relationships and sex can play a significant role. However, women tend to be more self-critical and maintain a clearer sense of self than men, and their ability to adapt to schizophrenia may be slightly better than that of men [25].

Conclusions

1. Schizophrenia is a genetically determined disease.

2. An important role in the etiology and pathogenesis of schizophrenia is played by transmitters – dopamine, serotonin, GABA. Violation of the synthesis of dopamine, serotonin, GABA or damage to the organs synthesizing them leads to the disease symptoms appearance. The role of melatonin in the pathophysiology of this disease is discussed, but there is no reliable research base.

3. Schizophrenia is often accompanied by organic damage, which is proven by MRI and CT of the brain. This is manifested by changes in the lateral ventricles, fourth ventricles and the cerebral cortex, namely the frontal and temporal lobes.

4. Schizophrenia may be caused by an autoimmune process, which is confirmed by changes in the cytokine profile, as well as the number of T- and B-lymphocytes.

5. The risk of schizophrenia increases with the presence of the following psychodynamic factors in the patient's life: psychological trauma in childhood and adolescence, sexual trauma, domestic violence, high levels of stress.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 06/02/2023
Revised version received: 12/18/2023
Accepted: 01/15/2024

Please cite this article in English as: Vanyukov V.V., Gulyaeva I.L., Ganeeva E.R., Sukhanova O.S., Zhvakina E.A., Minkhazeva E.M., Baluyeva T.A. Current understanding of the etiology and pathogenesis of schizophrenia. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 42-51. DOI: 10.17816/pmj41242-51

Scientific Review
UDC 618.2
DOI: 10.17816/pmj41252-60

PROBLEMS OF TEENAGE PREGNANCY: OBSTETRIC AND PERINATAL OUTCOMES

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ПРОБЛЕМЫ ПОДРОСТКОВОЙ БЕРЕМЕННОСТИ: АКУШЕРСКИЕ И ПЕРИНАТАЛЬНЫЕ ИСХОДЫ

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The review describes the problems of teenage pregnancy. A characteristic feature of the course of gestation in adolescents is a significant number of complications accompanying it. The problem of teenage pregnancy should be prevented not only by medical professionals, but also regulated by means of appropriate legal, social and economic measures.

Management of young first-time mothers` pregnancy should be based on earlier consultative follow-up and planned hospitalization for targeted treatment of complications, as well as a thorough risk assessment during gestation and childbirth.

Keywords. Teenage pregnancy, pregnancy in adolescents, pregnancy in young people.

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В обзоре описаны проблемы подростковой беременности. Характерной особенностью течения гестации у подростков является значительное число осложнений, сопровождавших ее. Проблема подростковой беременности должна предотвращаться не только силами медицинских работников, но и регулироваться при помощи надлежащих мер правового, социального и экономического характера.
Оптимизация тактики ведения беременности у юных первородящих должна основываться на более раннем консультативном наблюдении и плановой госпитализации для целенаправленной терапии осложнений, а также тщательной переоценки риска в течение гестации и родов.
Ключевые слова. Подростковая беременность, беременность у подростков, беременность у юных.

The outcome of pregnancy is determined by the reproductive, gynecological and somatic health of the woman. In turn, reproductive and gynecological health depends on reproductive behavior. Today, young people often engage in premarital sexual relations, change sexual partners, which can negatively affect the state of the woman's reproductive system and lead to premature termination of pregnancy, unfavorable outcomes and secondary infertility [1].

Acceleration is accompanied by a tendency towards early onset of menarche [2–4].

Early onset of menarche in the absence of sexual education is accompanied by early onset of sexual activity and undesirable consequences: the onset of pregnancy at a young age, which has unfavorable outcomes – from premature birth to perinatal and maternal mortality [5; 6]. At the same time, there is a high risk of contracting sexually transmitted infections [7]. An important problem in the organization of obstetric and gynecological care in the Russian Federation is pregnancy and childbirth in first-time mothers under the age of 18 [8].

PREVALENCE OF TEENAGE PREGNANCY

Young first-time mothers account for up to 11 % of births worldwide [8; 9]. Early pregnancy affects countries with different income levels. However, its probability is higher in developing countries, where 21 million gestations are registered annually in girls under 18, half of which are unwanted, and about 800 thousand births occur in girls under 16 [10–12]. In poor countries, 13 % of girls are married before the age of 16, and 39 % before the age of 18 [13], which increases the birth rate in this category. The proportion of these girls decreases with increasing education level – from 34 % among the uneducated to 19 % among those with primary education and 8 % with secondary education [14]. It is worth noting that young mothers are at high risk of repeated pregnancy with short intervals between each child [15–17].

The medical and social portrait of young first-time mothers can be described as follows: early menarche, premature onset of sexual activity, sexual violence, low standard of living in the family, lack/low level of education and desire to obtain it, unwillingness to assess the consequences of their actions, neglect of contraception methods, as well as insufficient quality of medical care in the family planning system [9].

According to some data, of those who gave birth in adolescence, only 30 % were university students, about 70 % had a secon-

dary school education, of which 44.2 % were housewives [15]. According to other studies, the contingent of young first-time mothers consisted of 59 % schoolgirls, 42 % lyceum and college students, with bad habits in 6–17 % of respondents. The occurrence of repeated pregnancy at the age of under 19 indicates the ineffectiveness of contraception and family planning measures [15]. Low levels of contraceptive use are due to a lack of knowledge among young girls about where they can get contraception and how to use it correctly [18].

RISK FACTORS FOR PREGNANCY IN ADOLESCENTS

A number of factors contribute to teenage pregnancy: lack of information, lack of sex education, early marriage, sexual violence, low levels of knowledge and access to contraception, and lack of necessary legislative measures [19]. Sexual violence accounts for 30 % of the causes of unwanted pregnancy [20; 21]. As a result, this leads to a decrease in the number of women of reproductive age, a decrease in their reproductive potential, complicated pregnancy, infertility, and a decrease in the birth rate, the onset of which begins in adolescence [20].

Childbirth at a young age increases the risks for mothers and babies. There is an opinion that young age helps to overcome the physiological and medical difficulties of childbirth [22]. At the same time, obstetricians-gynecologists and neonatologists believe that teenage pregnancy carries a risk of disruption of fetal development, and childbirth often proceeds pathologically due to the immaturity of physiological processes and requires instrumental or surgical intervention during childbirth [23–26].

Although young first-time mothers are somatically healthier than older women, they often have a body mass deficit [9]. Sexually transmitted infections are more often registered in the group of girls aged 13–18 years, which is probably associated with frequent changes of sexual partners and the absence of contraception. Therefore, the age of pregnant women under 18 years should be considered as a perinatal risk factor [15].

In some cases, inadequate behavior of the young woman during pregnancy, a negative attitude towards examination and prenatal care, poor nutrition, alcohol and drug use are observed [27]. Girls who have been subjected to violence have mental deviations, behavioral and emotional disorders, which negatively affect the upbringing of children in such teenage mothers [28; 29].

CONSEQUENCES OF TEENAGE PREGNANCY

Pregnancy in young women is associated with a higher risk of socioeconomic and health consequences. Pregnancy complications in young women are almost 2.5 times higher than in adult women, and the number of complications during childbirth is 1.7 times higher [30; 31]. Complications such as threatened miscarriage, vomiting during pregnancy, severe hypertensive conditions, premature rupture of mem-

branes and premature birth, respiratory distress syndrome, fetal growth retardation, and neonatal pathology are recorded. Such girls have an increased risk of developing eclampsia, postpartum endometritis, and other infectious complications [21; 33–36]. Only 30 % of births in adolescents are physiological, while in other cases instrumental intervention is required [15]. Obstetric complications are the leading cause of maternal mortality in young first-time mothers worldwide [21]. The risk of maternal mortality in adolescents correlates with socio-demographic factors: low socio-economic status of the family, low level of education, insufficient prenatal care [32].

One of the main causes of adverse obstetric outcomes in young women is gestational hypertension, the incidence of which in adolescents is up to 18 % [37–42]. Complications associated with gestational hypertension lead to hypoxic-ischemic damage to the fetal brain [43; 44]. During pregnancy, the intensity of biochemical and metabolic reactions increases, the result of their side effects can be an increase in primary free radicals and activation of the lipid peroxidation process, which has a damaging effect on the cell [45]. The Apgar scores of newborns from young mothers are lower than those from mothers of reproductive age, and children with low birth weight are more often born [40; 41].

According to some data, the most common pathologies in newborns from young mothers with preeclampsia are chronic hypoxia, fetal growth retardation, prematurity, respiratory distress syndrome, asphyxia, and cerebral disorders. The risk of infant death in children from young mothers is 1.5 %. At the same time, the increased frequency of perinatal complications is largely associated not with the young age of first-time mother, but with such social risk factors as bad habits, complicated somatic and obstetric-gynecological history [46]. The high level of infant mortality is also largely associated with a significant level of premature births in adolescents [28; 44]. Serious complications are facilitated by rapid and precipitous labor, polyhydramnios, and a contracted pelvis. Biological immaturity of the body of teenage mothers leads to unfavorable obstetric and perinatal outcomes, accompanied by the birth of low-weight newborns and lower scores on the Apgar scale [47; 48].

PREVENTION OF TEENAGE PREGNANCY

The problem of teenage pregnancy should be regulated and prevented using social, economic and legal measures [13; 49]. The World Health Organization, in close cooperation with international organizations, has identified measures to reduce the number of marriages concluded before the age of 18, which should be aimed at girls receiving a full school education, raising the culture of behavior and prohibiting early marriage [50]. In order to reduce the number of pregnancies in girls under the age of 19, it is necessary to increase knowledge about fertility, create

public support for young women, conduct sex education for adolescents, work with local communities, and intensify communication between parents and children on the topic of sexual development [51; 52]. Other measures to prevent teenage pregnancy include the adoption of legislation ensuring free access to contraception and the fight against sexual violence. Preventive action, counteracting unplanned and teenage pregnancies can be effective if work is strengthened in schools. Optimization of pregnancy management tactics in young first-time mothers should be based on earlier consultative follow-up, risk assessment of the gestation period and planned hospitalization to prevent the development of complications during childbirth [28].

Conclusions

Thus, pregnancy in adolescent girls is a serious medical and social problem. The reasons for the onset of pregnancy in adolescents are early onset of sexual activity, lack of sufficient knowledge about the reproductive system and low level of contraceptive use. Pregnancy that occurs at a young age is often terminated, increasing the risk of secondary infertility and adverse outcomes of subsequent pregnancies. The problem of teenage pregnancy should be prevented not only by medical professionals, but also regulated by means of appropriate legal, social and economic measures. Optimization of pregnancy management tactics in young first-time mothers should be based on earlier consultative follow-up, risk assessment of the gestation period and planned hospitalization to prevent the development of complications during childbirth.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 10/30/2023
Revised version received: 03/06/2023
Accepted: 03/25/2024

Please cite this article in English as: Kravchenko E.N., Shevlyukova T.P., Beznoshchenko G.B., Bulatova I.A. Problems of teenage pregnancy: obstetric and perinatal outcomes. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 52-60. DOI: 10.17816/pmj41252-60

Scientific Review
UDC 616.853-06: 616.891.6
DOI: 10.17816/pmj41261-67

SPECIFIC DYSPHORIC DISORDERS IN EPILEPSY

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СПЕЦИФИЧЕСКИЕ ДИСФОРИЧЕСКИЕ РАССТРОЙСТВА ПРИ ЭПИЛЕПСИИ

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To analyze affective-somatoform (dysphoric) disorders specific to epilepsy.
Dysphoric disorders can be divided into 3 groups: "periictal" disorders, interictal dysphoric disorder and alternative affective-somatoform syndromes. There are 3 groups of risk factors for affective disorders in epilepsy including depressive and dysphoric: those associated with the disease, those associated with the treatment and those associated with psychosocial aspects. Treatment for depression in epilepsy includes medication and psychotherapy. At the first stage of drug therapy, anticonvulsants are corrected, and at the second, an antidepressant is added. Cognitive behavioral therapy is the most effective method of psychotherapy.
Dysphoric disorders in epilepsy are presented by a wide range of conditions, both paroxysmal and non-paroxysmal, and have their own classification and development factors, which must be taken into account when choosing adequate therapy.
Keywords. Epilepsy, affective disorders, dysphoria, depression.

Осуществлен анализ данных, связанных с аффективно-соматоформными (дисфорическими) расстройствами, специфичных для эпилепсии.

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Дисфорические расстройства можно разделить на три группы: «периктальные» нарушения, интериктальное дисфорическое расстройство и альтернативные аффективно-соматоформные синдромы. Выделяют три группы факторов риска аффективных расстройств, в том числе депрессивных и дисфорических, при эпилепсии: связанные с болезнью, связанные с лечением и связанные с психосоциальными аспектами. Лечение депрессии при эпилепсии включает медикаментозную терапию и психотерапию. На первом этапе медикаментозной терапии проводится коррекция антиконвульсантов, а на втором – добавляется антидепрессант. Из методов психотерапии наиболее эффективна когнитивно-поведенческая терапия.

Дисфорические расстройства при эпилепсии представлены широким спектром состояний как пароксизмального, так и непароксизмального характера, имеют свою классификацию и факторы развития, что необходимо учитывать при выборе адекватной терапии.

Ключевые слова. Эпилепсия, аффективные расстройства, дисфория, депрессия.

The frequency of epileptic seizures and affective disorders is the most important factor in the deterioration of the quality of life of patients with epilepsy. According to a meta-analysis conducted in 2021, the overall prevalence of depression among people over 18 years of age with active epilepsy was 32 %. Moreover, the frequency of depression has doubled in recent years: 16 % in 2000–2005 versus 35 % in 2016–2020 [1]. The types of affective disorders associated with epilepsy are most fully represented in the classification proposed by the International League Against Epilepsy (ILAE) in 2007 [2]. There are affective-somatoform (dysphoric) disorders specific to epilepsy, which we will consider in detail below, and affective disorders comorbid with epilepsy (dysthymia, mild or major depression, etc.), that we will not go into.

It is necessary to recall that the term "dysphoria" (from the Greek *dysphoria* – "irritation", "annoyance") is an antonym of the word "euphoria" and is usually interpreted as a melancholy-angry mood. The founder of the nosological approach in psychiatry E. Kraepelin described periodic dysphorias called Verstimmungszustand as the most common mental disorders in epilepsy back in 1923 [3]. Dysphoria is diagnosed in the presence of at least three of four symptoms: internal tension, irritability, aggressive behavior and hostility [4].

Specific mood disorders in epilepsy are more conveniently classified based on their temporal relationship with epileptic seizures. Affective-somatoform (dysphoric) disorders specific to epilepsy can be divided into three groups: "periictal", i.e. located "around" the seizure, interictal dysphoric disorder and alternative affective-somatoform syndromes. The term "ictus" (from the Latin *ictus* – "blow") is a synonym for the word "seizure". "Periictal" and interictal dysphoric symptoms are similar to each other and differ only in the presence or absence of a relationship between dysphoria and seizures [5]. "Periictal" dysphoric disorders (DD), in turn, are divided into three subgroups: prodromal ("preictal") DD, DD as a manifestation of epileptic seizures and postictal DD.

Prodromal (preictal) DD is experienced by up to a third of patients with temporal lobe epilepsy, most often it occurs before secondary generalized seizures [6; 7]. Among the dysphoric symptoms, anxiety and irritability predominate, occurring several hours, less often – days before the onset of the sei-

zure [8]. After the epileptic seizure, these disorders usually disappear. Preictal depression is considered as a manifestation of subclinical epileptiform activity or is explained by the activation of biological mechanisms involved in the development of both pathological conditions: depression and seizure [9].

DD as a manifestation of epileptic seizures is represented by affective non-motor focal seizures. They most often occur in mesial temporal lobe epilepsy. For them, as for other types of seizures, three clinical signs are characteristic: suddenness (but provocateurs are possible), stereotypy (but polymorphism is possible) and short duration (but the development of postictal disorders or epileptic status is possible). Affective seizures can occur in the form of paroxysmal anxiety, panic-type fear, dysphoria, anger and rage, agitation with aggression; euphoria occurs less frequently.

Postictal DD occurs in the first 72 hours (three days) after an attack or series of attacks. It occurs in patients with poorly controlled focal seizures. Among the postictal symptoms, in addition to irritability and depressed mood, there are anxiety and neurovegetative symptoms and / or cognitive disorders, psychotic disorders occur less frequently. The origin of this type of depression is associated with inhibitory mechanisms involved in stopping the attack [9].

The second group of DD specific to epilepsy is interictal dysphoric disorder (IDD). The best-known test for early detection of IDD and its differentiation from periictal mental disorders is the Interictal Dysphoric Disorder Inventory (IDDI) proposed by M. Mula et al. [10]. It consists of 38 questions grouped into eight sections by the number of IDD symptoms. The eight main IDD symptoms are combined into three large groups: affective symptoms (anxiety, fear), depressive symptoms (depressed mood, anergia, pain, insomnia), and specific symptoms (paroxysmal irritability and, rarely, euphoria). To diagnose IDD, at least three symptoms out of eight of “moderate” or “severe” degree, causing “moderate” or “severe” distress are required [11]. It is important to note that this test is a screening test and does not replace a clinical examination.

To identify depression in patients over 18 years of age, neurologists have also proposed the “Neurological Questionnaire of Depressive Disorder in Epilepsy”, consisting of only six questions, the Russian version of which was validated by M. Zinchuk et al. in 2020 [12]. The assessment of patients' responses varies from 1 to 4 points. The optimal point for identifying a current depressive episode is more than 12 points.

To quantitatively assess the dynamics of depressive manifestations, the Hamilton Depression Rating Scale (HDRS/HRSD) is used [13]. Testing is performed by a clinician. 17 signs are an indicator of the severity of depression. Four additional signs carry information about auxiliary symptoms that may require special treatment.

IDD usually occurs two years or more after the onset of epilepsy. Episodes of dysphoria occur without external provocateurs, last from several hours to two days and recur at intervals from several days to months [14]. However, it should be clarified that some interictal disorders may be indistinguishable from periictal ones [14]. The very existence of IDD is still a subject of controversy [15], and some authors believe that IDD as a nosological diagnostic unit is questionable

[7; 16]. It is also important that the clinical manifestations of IDD are very similar to premenstrual dysphoric disorder, and in women with epilepsy this can be a source of errors [17]. IDD is considered a risk factor for sudden suicide attempts and interictal psychoses [9; 18]. Epileptic schizophrenia-like psychoses are a more severe form of IDD [7].

The third group of DDs specific to epilepsy are alternative affective-somatoform syndromes. Synonyms for this term are: the phenomenon of forced (violent) normalization of the EEG (Landolt syndrome), described by H. Landolt in 1953 [19], and "alternative psychosis" in patients with epilepsy [20]. The phenomenon of forced normalization of the EEG is the emergence of psychopathological disorders associated with the cessation of epileptic seizures, occurring in a patient with uncontrolled epilepsy when changing antiepileptic therapy after establishing control over seizures (remission for at least a week) and normalization of the EEG (a decrease in the number of spikes on the EEG by half) [21]. The nature of this phenomenon has not been fully clarified. The following hypotheses are considered for its origin: subcortical (deep) EEG discharges, changes in the balance of neurotransmitters or a decrease in the level of folic acid, a specific type of channelopathy, etc. Possible manifestations of Landolt syndrome are: anxiety, depression, dysphoria, ADHD in children; derealization, depersonalization and schizophrenia-like manifestations; twilight disorder of consciousness.

The causes of affective disorders, including depressive and dysphoric disorders, in epilepsy can be divided into three groups: those associated with the disease, those associated with the treatment and those associated with psychosocial aspects. Among the factors, associated with the disease, the localization of the epileptic focus is dominant. Depression often develops with a focus in the left temporal lobe [22], and postictal mania – with the involvement of the frontal lobe of the non-dominant hemisphere [23].

Factors, associated with the treatment, are divided into two subgroups: prescription of antiepileptic drugs (AEDs) with a "depressogenic" effect (phenobarbital, topiramate, vigabatrin, tiagabine) and/or discontinuation of mood-correcting AEDs (carbamazepine, lamotrigine, valproates) [9]. Mood disorders occur significantly more often in individuals with uncontrolled epileptic seizures with antiepileptic therapy [24].

Factors associated with psychosocial aspects include: rejection and poor adaptation to the diagnosis, unpredictability of the disease course; the need to change lifestyle, prohibition of driving, forced change of job; lack of social support, less often – discrimination based on the diagnosis and other circumstances [25].

Treatment of affective disorders, including depressive disorders, in epilepsy should combine two directions: drug therapy and psychotherapy. Drug therapy is carried out in two stages [9]. At the first stage, correction of AEDs is necessary in order to achieve seizure control and possible replacement of AEDs with a "depressogenic" effect with mood-correcting AEDs. AEDs are used to normalize mood in patients with epilepsy in three cases: if depressive symptoms (including interictal DD) have a temporary connection with recurrent seizures and / or they appeared after the introduction or increase in the AEDs dose with a negative psychotropic

profile, and / or they appeared after the cancellation of mood-correcting AEDs [26].

At the second stage of drug therapy for depression, an antidepressant is added. There are three principles for prescribing antidepressants for epilepsy: choosing a drug with a minimal proconvulsant effect, low doses in the initial period of treatment, slow titration to target doses. Preference is given to selective serotonin reuptake inhibitors (SSRIs): fluoxetine for anergy; sertraline, citalopram for insomnia [27; 28]. Agomelatine can be prescribed, especially with desynchronization of circadian rhythms. Classical antidepressants (tricyclics) are almost never used to treat mood disorders in epilepsy, since their use is associated with the risk of increasing the frequency of epileptic seizures. The duration of treatment with antidepressants is from three to six months, followed by gradual withdrawal of drugs.

Psychotherapy for depression in epilepsy (including online self-treatment programs) is underused, although it has proven its effectiveness [29]. A meta-analysis of 13 studies examining cognitive behavioral therapy (CBT) for depression in epilepsy found that CBT was effective in reducing depression and improving quality of life, but was ineffective in controlling seizures [30].

Conclusions

Affective-somatoform (dysphoric) disorders specific to epilepsy can be divided into three groups according to their temporal relationship with epileptic seizures: "periictal" disorders, interictal dysphoric disorder, and alternative affective-somatoform syndromes (Landolt syndrome). "Periictal" dysphoric disorders, including prodromal ("preictal"), ictal, and postictal disorders, are closely related to the type and frequency of seizures. Interictal dysphoric disorder is actively studied, but its existence as a nosological diagnostic unit is still a matter of debate. The pathogenesis of Landolt syndrome is not fully understood. Treatment of depression in epilepsy should include both drug therapy and psychotherapy. At the first stage of drug therapy, anticonvulsants are adjusted in accordance with the identified type of disorder, and at the second stage, an antidepressant is added. Of the psychotherapy methods, cognitive behavioral therapy is the most effective. Thus, affective disorders in epilepsy are represented by a wide range of dysphoric psychopathological conditions of both paroxysmal and non-paroxysmal nature, have their own classification and development factors, which must be taken into account when choosing adequate therapy.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 11/14/2023
Revised version received: 12/13/2023
Accepted: 03/25/2024

Please cite this article in English as: Malov A.G., Andrusenko A.A., Selyanina N.V. Specific dysphoric disorders in epilepsy. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 61-67. DOI: 10.17816/pmj41261-67

Scientific Review
UDC 614
DOI: 10.17816/pmj41268-79

PROFESSIONAL RELIABILITY OF PERSONNEL AND CORPORATE WELLNESS PROGRAMS

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ПРОФЕССИОНАЛЬНАЯ НАДЕЖНОСТЬ ПЕРСОНАЛА И КОРПОРАТИВНЫЕ ПРОГРАММЫ КОМПЛЕКСНОГО БЛАГОПОЛУЧИЯ

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To consider the key aspects of providing professional reliability of the personnel and their connection with the health preservation programs and transformation into corporate wellness programs. The importance of a healthy lifestyle is generally recognized. At the same time motivating employees to a healthy lifestyle is generally considered to be a complex task as well. The need to shift towards a comprehensive approach is noted, the development of corporate well-being programs aimed at supporting and improving the physical and psychological health of employees in particular, as well as enhancing their professional skills and qualities. This becomes a strategic move for the company, aimed at creating a healthy and supportive environment. Moreover, the development of such programs may not only be a business initiative but also align with the trends of

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the state policy of the Russian Federation. It can be confidently stated that the issue requires further discussion and exploration.
A balanced approach to professional training, motivation, psychological support, and health programs is a key to creating a productive and steady labor potential for the enterprise.
Keywords. Corporate well-being programs, health programs, engagement, professional reliability of personnel.

Рассмотрение ключевых аспектов обеспечения профессиональной надежности персонала и их связь с программами сохранения здоровья в контексте трансформации в корпоративные программы комплексного благополучия. На фоне общего признания важности здорового образа жизни существует признание того, что мотивирование сотрудников к активному ведению здорового образа жизни представляет собой сложную задачу. Отмечается потребность перехода к комплексному подходу, а именно разработки корпоративных программ благополучия, направленных на поддержание и улучшение физического и психологического здоровья работников, а также на развитие их профессиональных навыков и качеств, что становится стратегическим шагом для компании, направленным на создание здорового и поддерживающего окружения. Кроме того, разработка таких программ может быть не только инициативой бизнеса, но и следование трендам государственной политики РФ. Можно с уверенностью утверждать, что вопрос нуждается в дальнейшем обсуждении и изучении.
Сбалансированный подход к профессиональному обучению, мотивации, психологическому сопровождению и программам здоровья является ключом к созданию продуктивного и устойчивого трудового потенциала предприятия.
Ключевые слова. Корпоративные программы комплексного благополучия, программы здоровья, вовлеченность, профессиональная надежность персонала.

At the present stage of labour resources development and improvement, there is an uneven distribution of the labour force across the most developed industrial regions. Volga Federal District shows the largest decrease in the labour force, the Central Federal District has almost no change in the number of workers, and in the North Caucasus Federal District it is increasing. For 2022 – there is a decline in the population of Perm Krai, compared to 2021, by 48,613 people, including urban population by 42,251 people.

Aging processes in the labour force are evident, particularly due to the movement of the smaller generations of the 1990s and early 2000s into the working age group and the increase in the labour activity of the older generations. The share of workers under 40 will decrease from 42.0 % in 2019 to 37.4 % in 2030. Demographic changes will produce a multidirectional impact on the number and structure of the labour force in different regions of Russia. These changes will depend on economic activity of older age groups and the ability of regions to attract migrants, both domestic and international. At the same time, the ageing of the labour force is a serious challenge for the Russian economy [1]. The mortality rate of working age people in 2022 in Perm Krai amounted to 9036 people (100 %), the structure of causes of death is as follows: circulatory diseases – 30.7 %, neoplasms – 13.2 %, external causes – 24.8 %, other causes – 31.3 %. Cardiovascular pathology takes the leading position in causes of mortality [2].

Perm Krai constitutes a significant share of the national industrial production. It is

home to large industrial complexes, including chemical, petrochemical, metallurgical, aviation and machine-building industries, as well as power and construction facilities. Perm Krai holds resources for mining minerals such as oil, potassium salts and hard coal. There are 67 large industrial enterprises and 404 medium-sized organisations on the territory of Perm Krai (7.3 % of the total number of enterprises in Perm Krai). These industries shape the environment and have a direct impact on the health of the population. Labour conditions at industrial enterprises of Perm Krai have been unfavourable for a long time practically in all spheres. This leads to occupational diseases among working people of working age as well as their disability [3]. At the same time, the share of preventive medical examination coverage remains consistently high – 98 %. In 2022, only 36 people were diagnosed with occupational diseases for the first time (total number of diseases – 37), including:

– length of service (contact with hazardous factors): less than 10 years – 4.3 %, 11–20 years –19.4 %, 21–30 лет – 30.6 %, more than 30 years –44.4 %;

– by age: up to 40–13.9 %, 41–50 years old – 25 %, 51–60 years old – 38.9 %, above 60 – 22.2 %;

– by sex: men – 63.9 %, women – 36.1 % [4].

Health of workers is determined not only by workplace hazards, but also by social and individual factors and the availability of health services. Considerable improvements in industrial safety have been made in recent decades. Assessing the risks of chronic non-communicable diseases, health screenings, safety training, use of protective equipment and workplace improvements all contribute to safer workplaces [5]. Successful implementation of new technologies and good labour culture led to a significant reduction in the exposure to adverse occupational factors that can cause occupational diseases. However, the workload and intensity, as well as the level of psycho-emotional stress increased in parallel. This new environment of adaptation may contribute to the formation of corticovisceral malfunction and autonomic nervous system imbalance. This leads to an increased risk of developing psychosomatic pathology or aggravating the existing functional changes in organ systems. The cardiovascular system is highly susceptible to psycho-emotional stress [6].

Unfortunately, the introduction of market relations in the production sphere is not followed by employers' efforts to ensure safe and healthy labour conditions to protect the health of workers and the population as a whole. Based on medical statistics in Russia, only 20 % of computerised workplaces meet modern safety standards.

Research on the health effects of computers produces mixed conclusions, ranging from claims of absolute safety to suggestions of possible genetic risk. Periodic medical check-ups of this group of workers revealed various deviations in their state of health. It is worth noting that there is not yet a clear systemic response of the organism to exposure

to computer related factors, and the diagnostic package at the level of preclinical disorders has not been developed [7] In 2022, 610 thousand inhabitants of the Perm Krai underwent preventive examinations and check-ups of the adult population, of which more than half (54 %) were citizens of working age. In 2022, almost 30,000 people who underwent check-ups were diagnosed with chronic diseases for the first time. 52 per cent of diseases of the circulatory system and 56 per cent of malignant neoplasms were detected during the check-up among persons of working age.

Nowadays, when the dynamic nature of business processes and market competition require high professional reliability of personnel [8], it becomes essential to highlight the theoretical fundamentals and practical approaches in this area. Personnel reliability in carrying out their duties is fundamental to run business successfully [9].

Recent global health statistics show alarmingly high levels of numerous key risk factors for non-communicable diseases (NCDs). Almost one in four people in the world continues to use tobacco. Adult activity leaves much to be desired, with one in four adults lacking adequate levels of physical activity. Obesity and hypertension problems are gaining momentum worldwide [10].

To develop the theoretical basis for professional credibility, several key aspects have been considered.

Personnel professional reliability plays a key role in the effective business running. It is widely recognized that a reliable workforce is an important element in the success of any business, ensuring that it achieves its objectives [11].

Within this context, it is critical to understand the various factors affecting personnel professional reliability and to develop methods and techniques to ensure this credibility, including through the implementation of corporate wellbeing programmes.

A.A. Shalimov's research article "Professional training as a method of labour motivation of personnel" considers the effect of training and development on personnel productivity [12]. The author claims that training and development programmes can increase the personnel professional reliability by teaching them the necessary skills and knowledge to perform their functions successfully, and that professional training is undeniably a powerful incentive to motivate employees, provided that the process is properly managed. Based on the concept of building career paths, it is essential to select educational programmes with care, taking into account the individual particular features of each labour group.

Each team member is seen as a unique balance of being a career manager and owner of unique personality traits. This emphasizes the inherent importance of embracing individuality in the development of career plans. A careful study of the professional background, as well as the results of psychological assessment of personal, business and collective traits, becomes an indis-

pensable part of the determination of adequate individual development strategies.

It is a central task to identify the skills and knowledge for which a company is ready to reward its employees through training. The process of professional growth should align perfectly with the internal strategy of the company, and the actual set of knowledge provided by the company should be constantly evolving and diverse, without stagnation and providing the highest level of competence.

In the article " Personnel involvement – the main reserve for increasing the efficiency of modern companies" N.V. Gromova emphasizes that employee engagement is a critical factor contributing to the professional reliability of personnel [13]

N.V. Gromova emphasizes that employee engagement is a crucial factor contributing to the personnel professional reliability [13]. The author believes that engaged employees are more motivated for high performance and are ready to make a significant contribution to the success of the company. Low team cohesion can impede a company's high performance, and vice versa. There are a number of factors that rely on the terms and conditions offered by the company as an employer that influence the level of employee engagement. These can include career opportunities highlighting the value of employees, organizational processes, service recognition and reputation to the employer. Analysis of these factors can serve as a useful tool for company management and HR subdivisions in developing programmes to enhance employee engagement.

Thus, high level of the personnel involvement results in an innovative environment in the company that favours both the emergence of innovative ideas and faster implementation. This brings out the importance of managing the factors that influence involvement of the personnel, as a strategic area for arriving at the corporate success.

In the work of O.L. Osadchuk "Shaping the occupational reliability of a professional specialist" it is emphasized that, when raising the issue of the degree of reliability of professional activity, we enter the zones of not only labour psychology, but also professional education, where these two worlds are intertwined in a surprising pattern [14]. A specialist's professional training formation requires that his "backpack" "contains" self-regulation as a reliable tool that guarantees stability in his professional sphere. It is here when the importance of psychological support for vocational education, which, just like technology, facilitates the development of this credibility, comes into play. One of the key principles of this support is respect for the right of individuals to make their own decisions regarding their professional career development and to take responsibility for these decisions. The task of psychological support is limited to the provision favorable conditions to the full professional growth of the individual.

Pursuant to the concept of E.F. Zeer (2000), psychological support is seen as a

complex process of studying, shaping, developing and improving the professional growth of an individual. Thus, the psychological support technique of forming the professional activity reliability through the development of self-regulation includes three key stages: 1. Diagnostics of the learner's self-regulation level in the process of professional education. 2. Providing information about the fields and methods of self-regulation development. 3. Support and assistance in the development of learners' self-regulation in the process of vocational education and training. Efficient implementation of this technique becomes possible through the use of personality-oriented methods of vocational development, such as developmental psychodiagnostics, professional training and psychological consulting on issues of personal and professional growth. Ultimately, effective psychological support in the formation of professional activity reliability should become an inherent part of the integral process of personally oriented professional education.

The work of E.A. Rodionov "Psychological factors of efficiency of employees of a modern business" highlighted the fundamental components affecting the performance of the enterprise personnel [15]. One of the significant aspects that emerged was the focus on meeting the needs and expectations of all participants in the company, from shareholders to the company as a whole. Based on the assumption that efficiency is closely linked to the level of employee engagement, the importance of meeting their basic needs is emphasized.

One of the important models of motivation, based on the law of R.M. Yerkes and J.D. Dodson, reveals the relationship between the intensity of motivation and the quality of activity. The growth of motivation initially improves efficiency, until it reaches the optimal level, which is followed by a gradual decline in success.

Therefore, ensuring an optimal level of motivation, with due regard to the individual features of each employee, becomes an indispensable condition for harmonized labour activity and excellent results achievement.

The key aspect that stands out in achieving production growth is result orientation, including the company, group and individual components. Certain departments and employees are recognized as effective not only by achieving personal plans, but also when these achievements align with the company's overall objectives. The company-provided resources, including information, material, value and process, become the tools and the employee returns the result. The coincidence of both the employee's and the company's view towards the outcome is the basis for profit and loyalty. The important factor is the understanding of the result by each employee. If processes are clearly defined, the outcome tends to meet expectations. However, if goals and outcomes are not clearly defined, individual views of success may differ greatly, causing disintegration of efforts. The perfect situation exists if each employee understands

his or her role, conforms to it, and aligns his or her actions with a shared vision. However, when employees have different understandings of goals, they may face inconsistencies and even conflicts, creating a situation of "every man for himself".

The performance management strategy is intended not only to ensure ongoing performance, but also to develop employees. The employee's competence becomes the key element, which implies the ability to act in accordance with the company's goals and the position's standards, and possessing the personal qualities necessary to achieve results.

It is impossible to avoid such an important aspect as communication within the context of employee performance assessment. If there are no effective "vertical" and "horizontal" communication channels within the company designed to create a positive climate for ongoing dialogue between managers and team members, it can make it difficult to identify expectations and share information regarding the mission, values and goals of the company. Performance management, in turn, contributes to the development of the company by involving employees in the processes of defining their own goals and methods of achieving them.

Hence, employee efficiency is a deeper notion than just a productivity factor. It comprises a set of psychological factors that determine personal efficiency. Employee performance assessment cannot be considered apart from the context of the company. Success in one's personal field does not always transform to effectiveness for a particular company. An employee may excel in one company but be ineffective in another. It is important not only to understand but also to adopt the company's goals and objectives, and to work in a team where the common goal corresponds with the company's mission. An employee who can meet his or her needs in such an environment is often more effective.

K.Y. Yashkina in her research article "Health as the most important element of an employee's labour potential" attracts attention to the importance of health as the indicator of labour potential in view of three factors – the individual, the organization and society [16].

For an individual, health means not only the ability to work, but also the lack of forced sick leave due to health problems. It is a crucial factor that affects his personal performance and the overall outcome of his work life. At the corporate level, the health status of the personnel directly affects the amount of time lost due to employee illnesses and the additional expenses incurred by the company to maintain the health of its employees. Team Health Management is becoming a key factor for the company development.

At the level of the society, health affects life expectancy and the cost of a state's health care system. Health maintenance becomes an integral part of the social policy and employer's social responsibility. Nowadays, personnel health management is a crucial aspect of the company development

and improvement. Managers realize that employee health has a significant impact on work performance and therefore encouraging employees to maintain and improve their health gains priority [17]. However, in the current environment, traditional approaches to maintaining employee health, such as holding workplace exercises, promoting healthy lifestyles and providing VHI programmes, and holding sporting events, suffer from limitations, which entail inability to fully resolve the existing problems. Health initiatives considered apart from other activities prove insufficient to ensure comprehensive health promotion. Now we are facing the challenge to revise the traditional methods of influence and implement a comprehensive approach that includes preventive measures and maintaining the overall health of employees.

Thus, investment in personal health requires a comprehensive approach aimed at forming, maintaining and improving health. The scope of these investments depends on numerous factors. It is important to emphasize that the approach aimed at long-term economic impact transforms social expenditures into real investments and effective measures to maintain health and labour potential.

Against a common acknowledgement of the importance of a healthy lifestyle, there is a recognition that motivating employees to adopt an active healthy lifestyle is a challenge. Despite the fact that many people are aware of the importance of healthy lifestyles, not everyone follows these principles successfully. This emphasises the importance of creating conditions and establishing a supportive environment that would encourage employees to adopt healthier lifestyles [18].

Today, preserving health is becoming one of the main tasks of society and the responsibility of the employer. Companies should actively implement measures to prevent diseases and improve working conditions. The employer is responsible for striving to create a 'healthy workplace', taking into account the physical and psychosocial needs and lifestyles of employees. Only a comprehensive approach can prove to be an effective method of improving the health of employees and increasing overall labour productivity.

A healthy workplace (as defined by the World Health Organization's Healthy Workplaces: A Model for Action programme) is a place in which workers and managers collaborate to use a continual improvement process to protect and promote the health, safety and well-being of all workers, to contribute to the improvement of the workplace while managing major workplace challenges. The main theses include that the main efforts of both employers, employees and the state in the field of health promotion should be directed to [19]:

– Health and safety in the physical work environment;

– Health, safety and well-being in the psychosocial work environment, including workplace management and workplace culture;

– Personal health potential of the employee at the workplace;

– Ways to participate in joint work aimed at improving;

– Health of workers, their families.

Thus, the studies within the reference list confirm the importance of ensuring personnel professional reliability and describe various methods and factors that may affect this process.

Thus, the labour efficiency of an employee with preserved health poses a complex mosaic image, which is formed by the interaction of various factors and requires a systematic approach to human resource management [20]. A balanced and timely approach to professional training, motivation, psychological support and health is the key to establishing a productive and sustainable workforce in the company [21]. Employer-supported programmes that focus on health and safety at work play an important role in improving the overall well-being of employees. Active measures implemented in the daily business activities of companies contribute to the improvement of personnel health and, at the same time, reduce the risks of occupational diseases [22].

Thus, the development of corporate wellbeing programmes aimed at maintaining and improving the physical and psychological health of employees, as well as at developing their professional skills and qualities, becomes a strategic step for the company towards creating a healthy and supportive environment, which results in a win-win situation for both employees and the business as a whole. In addition, the development of such programmes can be both a business initiative and an observance of the trends of the Russian Federation's state policy. Increasing healthy life expectancy in Russia is a strategic objective for the period up to 2030. [23]. This goal can be achieved by improving the health of workers through the introduction of measures to correct risk factors in the workplace. The implementation of the motivation system of citizens towards a healthy lifestyle in the workplace is included in the federal project "Promoting Public Health" of the national project "Demography" [24].

With the introduction of corporate programmes, employers are obliged to create conditions to encourage employees to adopt healthy lifestyles, including quitting smoking and alcohol consumption, switching to a healthy diet and increasing physical activity. Tasks to preserve health, ensure the well-being of personnel, ensure safety in the field of occupational health and safety, as well as the implementation of comprehensive social programmes are included in the social block of the concept of sustainable development of the company (ESG), presented in the RSPP collection of corporate practices [25].

CONCLUSIONS

To ensure the long-term professional reliability of personnel, we need to revise traditional strategies and introduce innovative programmes focusing on disease prevention, physical activity and general health promo-

tion. Preventive measures aimed at health promotion, creation of conditions in which employees can fully develop, feel at ease in the team and successfully cope with professional challenges are becoming an integral part of corporate responsibility for personnel well-being. A common trend in corporate practice emphasises that companies that focus on the well-being of their employees tend to be more successful in attracting and retaining skilled people, which in turn strengthens their image as an employer of choice.

Following these conclusions, it is recommended that companies and organisations:

– Invest in vocational training: it is essential to develop training programmes that meet the needs of employees and the company and provide access to relevant knowledge and skills;

– Encourage motivation: creating motivational systems to address the individual needs of employees. Company values should be emphasised by providing career opportunities and recognition;

– Develop self-regulation: employees should be supported to develop self-regulation skills. This can be achieved through psychological support, training and the provision of a favourable working environment;

– Take care of health: introduce programmes to support health of employees. Wellbeing programmes should work to communicate not only the benefits of a healthy lifestyle, but also to create an environment in which taking care of health becomes a natural and valued part of the corporate culture. Such an approach, which focuses on establishing an environment for self-care, in addition to introducing health programmes, can remove barriers and make the path to a healthy lifestyle more affordable and available to a wide range of employees;

– Develop effective communication: encouraging open and effective communication within the company will help to identify expectations and ensure information exchange on key aspects of the company's culture and goals;

– Adopt a holistic approach: the worker should be regarded not only as a performer of duties, but also as a person, to integrate health care, training and motivation to form a productive and effective labour potential.;

– Involve employees in the process: employees should be encouraged to participate in decision-making, which enables them to actively influence their working environment and goals. This contributes to higher levels of engagement and responsibility.

Employers, by following these guidelines, can establish a healthy work environment that enhances employee performance and satisfaction, and consequently ensures a higher level of personnel professsional reliability.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

N.N. Malyutina – research concept, analysis of critical content.

K.V. Mudraya – literature data collection, analysis and generalisation of literature data, work with the manuscript text.

S.V. Luzina – methodological approaches example to ensure professional reliability of personnel.

Received: 01/29/2023
Revised version received: 03/28/2023
Accepted: 04/04/2024

Please cite this article in English as: Malyutina N.N., Mudraya K.V., Luzina S.V. Professional reliability of personnel and corporate wellness programs. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 68-79. DOI: 10.17816/pmj41268-79

METHODS OF DIAGNOSTICS AND TECHNOLOGIES

Scientific Article
UDC 616.66-089.31
DOI: 10.17816/pmj41280-86

MINIMALLY INVASIVE METHOD OF SURGICAL TREATMENT OF PEYRONIE'S DISEASE

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МАЛОИНВАЗИВНЫЙ СПОСОБ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЕЗНИ ПЕЙРОНИ

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Objective. To improve the results of surgical treatment of Peyronie's disease.
Materials and methods. 20 patients with Peyronie's disease aged 22 to 60 were treated in the urological departments of the Private Clinical Hospital “Russian Railways Medicine” and Astrakhan City Clinical Hospital

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No. 3 named after. C.M. Kirov. A method of surgical treatment of Peyronie's disease using a shortening technique without opening the tunica albuginea includes the application of a pressure tourniquet to the base of the penis, puncture of the cavernous bodies, injection of sterile saline into them until an erection is achieved, determination of the angle of curvature of the penis, removal of the tourniquet and surgery to eliminate curvature of the penis.
Results. Neither postoperative complications nor formation of hematomas were observed. The patients were discharged on the 4th day in satisfactory condition. 1.5 years` observation showed no progression of angular deformation of the penis which could impede sexual intercourse. The mobility of the skin of the penis was preserved.
Conclusions. In addition to the correction of penile deformity, our method eliminates the need for extensive incisions and preserves the physiological functions of the penis. As a result of using this surgical method, the following goals are achieved: minimal trauma to tissues in the surgical area, absence of scar processes in the plastic area and preservation of the skin of the penis mobility, absence of pronounced postoperative tissue edema, no need to drain the wound, reduction of the duration of the operation and minimal blood loss, short postoperative and rehabilitation period.
Keywords. Peyronie's disease, erectile dysfunction, penile deformity, surgical treatment.

Цель. Улучшение результатов хирургического лечения болезни Пейрони.
Материалы и методы. Пролечено 20 пациентов с болезнью Пейрони в урологическом стационаре ЧУЗ «КБ "РЖД-Медицина"» города Астрахань» и ГБУЗ Астраханской области «ГКБ № 3 им. С.М. Кирова». Возраст больных – от 22 до 60 лет. Способ хирургической коррекции болезни Пейрони по укорачивающей методике без вскрытия белочной оболочки включает в себя сдавление турникетом у основания полового члена, инъекцию в кавернозные тела стерильного физиологического раствора до достижения эрекции, расчет угла искривления полового члена, снятие турникета и операцию по устранению искривления полового члена.
Результаты. Осложнений после операции не наблюдалось. Не отмечалось образования гематом. Пациенты в удовлетворительном состоянии были выписаны на четвертые сутки. Отдаленные результаты в течение 1,5 лет показали отсутствие прогрессирования угловой деформации полового члена, затрудняющей проведение полового акта. Сохранялась мобильность кожи полового члена.
Выводы. Предложенный метод, помимо коррекции деформации полового члена, устраняет необходимость в обширных разрезах и сохраняет физиологические функции полового члена. В результате использования данного оперативного способа достигаются следующие цели: минимальная травматизация тканей в зоне оперативного вмешательства, отсутствие рубцовых процессов в зоне пластики и сохранение мобильности кожи полового члена, отсутствие выраженного послеоперационного отека тканей, отсутствие необходимости дренирования раны, сокращение длительности операции и минимальная кровопотеря, короткий послеоперационный и реабилитационный периоды.
Ключевые слова. Болезнь Пейрони, эректильная дисфункция, деформация полового члена, хирургическое лечение.

INTRODUCTION

The incidence of Peyronie's disease (PD), according to various researchers, ranges from 0.5 to 13 % [1–5], with men over 45 suffering more often. According to the data presented by P.A. Shcheplev, the PD prevalence in Russia ranges from 3 to 8 %, and according to autopsy data, it reaches 25 % [16]. To date, there is no consensus among authors on the pathogenesis of Peyronie's disease, so work continues in this direction, since there is no final verdict on the causes of the disease.

The theory of the development of Peyronie's disease as a consequence of the

erect penis trauma has received the greatest recognition. According to the proposed theory, hematomas in the tunica albuginea that occur after microtrauma lead to the development of plaques. It is known that the penis does not have an arterial network, but venous vessels intimately connected with the fibrous part of the tunica. With direct injuries and bruises or during active sexual intercourse, the membranes of the penis are traumatized, which leads to the development of aseptic inflammation. In turn, the inflammatory process inhibits the transformation of fibrinogen into fibrin, resulting in a decrease in the elasticity of the fibers of the protein membrane. Over the course of a year and a half, fibroplastic induration of the tissue develops, in which the degeneration of collagen cells progresses [6; 7].

Peyronie's disease is characterized by the following clinical manifestations: pain syndrome with curvature of the penis; palpated plaques or seals on the penis, erectile dysfunction.

The disease goes through two stages. In the first period, the patient is bothered by pain in the penis during and outside of erection. In the second stage, deformation and curvature of the penis occurs, making sexual intercourse difficult.

In Russia, many clinics use the classification of V.E. Mazo [8], which has four stages: Stage 1 – pain during erection, presence of plaques; Stage 2 – pain during erection and formations on the protein tunica; in the 3rd stage, denser fibers of the protein tunica are formed, in the 4th stage, calcifications are formed.

According to the classification of S. Barra and F. Iacono, used outside of Russia, the disease occurs in three periods: up to 6 months, up to a year and more. The degree of deformation of the penis depends on the size of the plaque and the angle of curvature. Mild deformation (curvature up to 30°, plaque up to 2 cm), moderate degree (60°, plaque up to 4 cm), severe degree (more than 60°, plaque more than 4 cm [9–11].

There are many methods of PD surgical treatment: shortening operations, plication techniques, lengthening operations, grafting using transplants, penile prosthetics in various modifications [20].

The main reason for contacting a urologist is discomfort in a man's intimate life as a result of penile curvature and pain syndrome.

During examination and collection of anamnesis, attention is paid to penile injuries, concomitant diseases, the size of the plaque, localization, and degree of deformation of the penis in an erect state are taken into account [12–14].

Surgical treatment of Peyronie's disease remains the most effective method of penile curvature correcting [15; 16].

Nesbit was the first to use shortening treatment method that includes opening the tunica albuginea, removing tissue on the opposite side of the penis in the form of an ellipse, with a general satisfactory result from 67 to 100 % [17]. Despite the positive results (79–100 % effectiveness), the operation has

a number of complications. This is a shortening of the penis, while erectile dysfunction after the operation occurs in 3.25–22.9 % of cases [4], loss of sexual function, according to literary data, reaches 12 % [9]. One of the modified methods of the Nesbit operation was proposed by P.A. Shcheplev, who invaginated the tunica albuginea without excision of the cavernous bodies [16]. In the 80–90s, D. Yachia and R.J. Lemberger made longitudinal incisions up to 1.0 cm in the zone of maximum curvature without excision of the tunica albuginea and sutured the wound in the transverse direction. According to the authors themselves, the effectiveness of the method ranged from 80 to 95 % [18].

Surgery with intracavernous phalloprosthetics using three-component prostheses is indicated for severe sexual dysfunction [19]. However, the analysis did not yield satisfactory results of plastic surgery using implants, since the high cost of prostheses and the risk of infection do not allow their widespread use.

Due to the fact that the search for new technological methods in the treatment of Peyronie's disease continues, there is a need for a differentiated approach to the choice of corporoplastic surgeries that can reduce the number of postoperative complications and improve treatment results.

MATERIALS AND METHODS

20 patients with Peyronie's disease aged 22 to 60 were treated in the urological departments of the Private Clinical Hospital "Russian Railways Medicine" and Astrakhan City Clinical Hospital No. 3 named after. C.M. Kirov from 2019 to 2022. Patients with a plaque size over 1.5 cm and an angle of curvature of the penis over 45° underwent surgical treatment.

A method of surgical treatment of Peyronie's disease using a shortening technique without opening the tunica albuginea is presented in the following stages: at the first stage a pressure tourniquet is applied to the base of the penis, a sterile saline solution (in a volume of 40–60 ml) is injected into the cavernous bodies until an erection is achieved, the angle of curvature of the penis is determined.

The second stage is to make three transverse skin incisions 0.3 cm long every 2 cm on the convex side of the penis on both sides of the urethra, then tunnel the subcutaneous space in the proximal direction from the coronary groove to the base of the penis above the cavernous body using a grooved Kocher probe (Fig. 1), after which a piercing needle with a non-absorbable thread (diameter 3–0) is inserted into the distal transverse skin incision, grasping the protein tunica to a depth of 3–5 mm, then this needle with the thread is punctured into the median transverse incision, then the needle with the thread is again punctured into the median transverse incision, grasping the protein tunica to a depth of 3–5 mm (Fig. 2). Then the needle with the thread is punctured into the proximal transverse incision, after which the needle is turned 180°, then the needle with the thread is passed subcutaneously through the formed tunnel to the

median transverse incision, and the free distal end of the thread is also passed to the median transverse incision through the tunnel, after which the ends of the thread are tied together, eliminating the deformation of the penis (Fig. 3), then all manipulations of the operation are repeated parallel to the first on the other cavernous body, after which all skin incisions are sutured with interrupted single sutures.

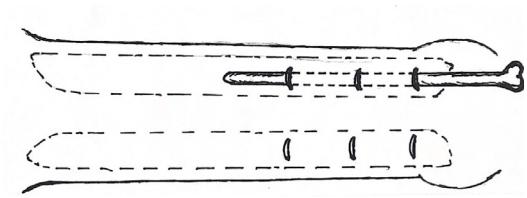

Fig. 1. Tunneling of the subcutaneous space with a grooved Kocher probe through transverse skin incisions over the cavernous body

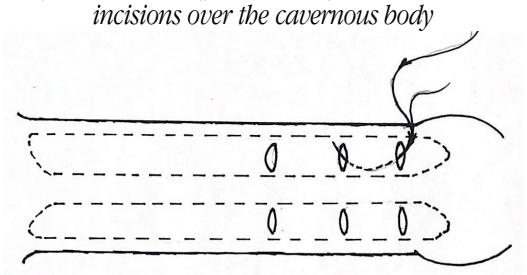

Fig. 2. Insertion of a piercing needle with a non-absorbable thread into a transverse incision of the skin with capture of the protein tunica to a depth of 3–5 mm

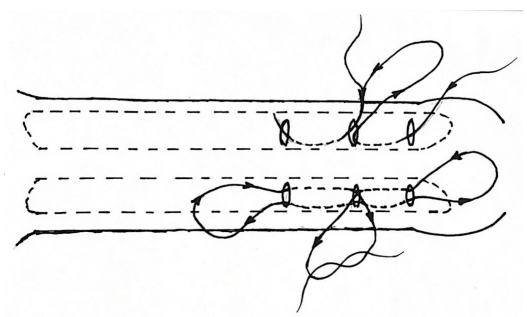

Fig. 3. Tightening and tying the ends of the thread together into a subcutaneous knot, elimination of penile deformity

RESULTS AND DISCUSSION

Neither postoperative complications nor formation of hematomas were observed. The patients were discharged on the 4th day in satisfactory condition. The patients abstained from sexual activity for 1.5 months. 1.5 years` observation showed no progression of angular deformation of the penis which could impede sexual intercourse. The mobility of the skin of the penis was preserved. The patients retained erectile function, pain syndrome during erection and curvature of the penis are absent. All patients are satisfied with the treatment results (in the form of an oral survey).

CONCLUSIONS

The proposed method (patent No. 2728937 dated August 03, 2020), in addition to the correction of penile deformity, eliminates the need for extensive incisions and preserves the physiological functions of the penis. As a result of using this surgical method, the following goals are achieved: minimal trauma to tissues in the surgical area, absence of scar processes in the plastic area and preservation of the skin of the penis mobility, absence of pronounced postoperative tissue edema, no need to drain the wound, reduction of the duration of the operation and minimal blood loss, short postoperative and rehabilitation period.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 11/28/2023
Revised version received: 03/14/2023
Accepted: 03/15/2024

Please cite this article in English as: Zurnadzhyants V.A., Kurashov D.V., Kchibekov E.A., Proskurin A.A. Minimally invasive method of surgical treatment of Peyronie's disease. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 80-86. DOI: 10.17816/pmj41280-86

Scientific Article
UDC 616.831-005
DOI: 10.17816/pmj41287-95

THE OPTIONS FOR PROGNOSIS OF THE OUTCOME OF ISCHEMIC STROKE IN YOUNG PATIENTS

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ВАРИАНТЫ ПРОГНОЗИРОВАНИЯ ИСХОДОВ ИШЕМИЧЕСКОГО ИНСУЛЬТА У ЛИЦ МОЛОДОГО ВОЗРАСТА

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Objective. To develop criteria for prognosis of the outcome of ischemic stroke, taking into account age, dynamics of state assessment, the Rankin and NIHSS scales readings and the fact of disability in the long-term period. The universal reliable criteria, that allow to predict the outcome of ischemic stroke, have not been developed yet.
Material and methods. The study group consisted of 246 patients with ischemic stroke aged 18 to 44 who were observed from 2008 to 2021.
Results. It is impossible to predict disability in a long-term period of ischemic stroke reliably. Predicting the outcome of ischemic stroke using the Rankin and NIHSS scales is significant in the acute period and allows to predict the dynamics of recovery in mild and moderate cases.
Conclusion. The predictive value of the integrative indicators of the patient's condition, assessed by the Rankin and NIHSS scales, has been established.
Keywords. Stroke, young age, mRS, prognosis.

Цель. Разработка критериев прогнозирования исходов ишемического инсульта (включая инвалидность) с учётом возрастного аспекта, динамики оценки состояния, показателей шкал Рэнкина и NIHSS. В настоящее время не разработаны универсальные достоверные критерии, позволяющие с высокой точностью предсказать исход ишемического инсульта у конкретного пациента.
Материал и методы. В период с 2008 по 2021 г. наблюдали 246 пациентов в возрасте от 18 до 44 лет включительно, перенесших ишемический инсульт.
Результаты. Достоверно спрогнозировать инвалидность в отдаленном периоде ишемического инсульта не представляется возможным. Благоприятные исходы ишемического инсульта в виде высокого уровня самообслуживания, а также сохранения трудоспособности возможны по показателям шкал Рэнкина и NIHSS в остром периоде.
Выводы. Установлена прогностическая ценность интегративных показателей состояния пациента, оцениваемых по шкалам Рэнкина и NIHSS.
Ключевые слова. Инсульт, молодой возраст, mRS, прогнозирование.

INTRODUCTION

The social consequences of ischemic stroke are currently one of the significant problems of modern society. Although most cases of stroke are diagnosed in the elderly, approximately 10 % of all onsets of the disease occur at a young age (the so-called "young" strokes) [1–4].

Ischemic stroke in young people causes limitations in the quality of life and professional status [5–7]. According to various sources, from 50 to 70 % of young people after an ischemic stroke return to work, and the period of time ranges from a few days after the stroke to 40 months, an average of 8 months. However, about 25 % of them need adjustments (another job or part-time work) in their profession due to their inability to perform their previous activities after a stroke, so less than half of patients return to their previous job [4–7].

There are no well-known risk factors indicating the likelihood of disability in the outcome of ischemic stroke in young patients [4–7]. Our research group attempted to predict a decrease in the level of disability in patients who have suffered an ischemic stroke using a combination of available anamnestic, clinical and laboratory data, assessment of the condition according to the Rankin and NIHSS scales readings [8–9] in the acute and long-term periods of ischemic stroke.

The objective of the study is to develop criteria for prognosis of the outcome of ischemic stroke (including disability), taking into account age, dynamics of state assessment, the Rankin and NIHSS scales readings.

MATERIALS AND METHODS

In the period from 2008 to 2021, 246 patients aged 18 to 44 years inclusive who had suffered an ischemic stroke were observed. Ischemic stroke was confirmed clinically and by neuroimaging results. On average, patients were observed for 6.18 ± 2.1 years. An analysis of the recurrence rate of vascular events and the frequency of deaths in the study groups, Rankin scale readings, analysis of the results of laboratory and instrumental research methods, as well as RMIS (Regional Medical Information System) data, the presence of disability (medical and social assessment certificate, extract from the certificate of examination of a citizen recognized as disabled, issued by the Federal Government Institution Main Bureau of Medical and Social Expertise) was performed.

To process the data, the mathematical method of linear discriminant analysis was performed using the Statistica 10.0 program.

RESULTS AND DISCUSSION

The universal criterion for assessing the severity of a condition after a stroke is the Rankin scale score (Modified Rankin Scale – mRS). We have assessed the results of recovery of patients after ischemic stroke in the long-term period (from 2 to 11 years) using this criterion (table).

The overwhelming majority of surviving patients ($n = 187$, 77.6 %) could be characterized in the period of residual effects as having a fairly high degree of self-care and minimal limitations in life due to the disease (0–2 on the Rankin scale).

We have recorded obvious positive dynamics in assessing the condition of young adult patients: in the period of residual effects, according to the Rankin scale, the number of patients who had 3–5 scores in the acute period decreased by 5.3 times (191 and 36, respectively).

A total of 47 recurrent acute cerebrovascular events were recorded in the observed group, including 35 ischemic strokes (74.5 %), with 3 patients developing 2 recurrent ischemic strokes each, 2 patients having 3 strokes, and 14 patients having fatal recurrent ischemic strokes. Transient ischemic attacks were observed in 9 patients (17.2 %). Hemorrhagic strokes were recorded in 3 patients (6.4 %), 2 of them against the background of taking anticoagulants, and one against the background of antiplatelet therapy; 2 patients died. Other acute ischemic events were recorded in 14 patients, of which 9 developed myocardial infarction.

It should be noted that there were no fatal outcomes during the inpatient stay in the patients we studied. A total of 23 patients (9.0 %) died during the observation period. The causes of death in the main group were recurrent ischemic stroke in

Dynamics of the severity of patients' condition in the acute and late periods based on the results of the Rankin scale assessment

Group	Rankin Score						
	0	1	2	3	4	5	6
The main group in the acute period (n = 248), abs. (%)	3 (1.2)	10 (3.90)	44 (17.2)	96 (37.5)	59 (23.0)	36 (14.1)	0
Main group at outcome (n = 246), abs. (%)	61 (24.8) *	82 (33.3) *	44 (17.9) *	20 (8.1) *	13 (5.3) *	3 (1.2) *	23 (9.4) *

N o t e: * – $p < 0.05$ when comparing the Rankin scale score in patients over time.

14 cases (60.9 %), hemorrhagic stroke in 2 cases (8.7 %) (in one of these patients, hemorrhagic stroke developed against the background of Fabry disease). 2 patients (8.7 %) died as a result of myocardial infarction. In 5 cases (21.8 %), the causes of death were other reasons (oncological diseases, bleeding of internal organs, diabetes mellitus, etc.).

Disability was established in 23.4 % (n = 60) of patients: group I – in 11 (18.3 %), II – in 23 (38.3 %), and III – in 26 (43.3 %). It is worth noting that the basis for establishing disability was not always neurological causes; in three young adults diabetes mellitus was the cause, one patient had mental disorders, and two had cardiovascular pathology.

In most cases, factors that can be regarded as obvious predictors of persistent impairment of life activity and social interaction in patients after a stroke remain unknown. Thus, we were faced with the task of predicting disability based on a combination of available anamnestic and clinical laboratory data.

To solve this problem, the research group selected prognostically significant features that were significantly different in patients at an atypical age who had not formed and formed persistent impairment of life activity and social interaction with the establishment of disability after the end of the recovery period of the disease. The use of the mathematical method of linear discriminant analysis made it possible to identify a set of features that characterized each variant of the outcome of ischemic stroke (disability or its absence) and to obtain a decision rule (IPI – integrative prognostic index), allowing each patient to be assigned to a certain group, when it is not known in advance which of the groups he belongs to. If, as a result of substituting the data of a specific patient into the decision rule, the IPI value is less than 0, then the patient is assigned to the group without disability, if the IPI is greater than 0 – then to the group that has formed disability.

In total, 14 parameters characterizing the anamnesis, clinical picture and laboratory data of the acute period of ischemic stroke were included in the analysis: gender, age, Rankin scale score in the acute period upon admission, NIHSS score, presence of an infarction focus according to CT (MRI) results in the acute period, involved vascular bed, ultra-

sound data of the brachiocephalic arteries (percentage of stenosis), lateralization of clinical symptoms in the acute period, glucose, fibrinogen, platelets levels in the acute period, significant changes in the ECG, pathogenetic type of stroke according to the TOAST criteria and the fact of smoking.

Based on the available data, an integrative prognostic index (IPI, *Z*) was formed using logistic regression by the formula:

$$Z = b_0 + b7Var7 + b8Var8,$$

where b_0 – 3.488881; *b*7 0.5727652; b8 0.07390234; *Var*7 – Rankin scale score upon admission to hospital in the acute period; *Var*8 – NIHSS score upon admission to hospital in the acute period.

Mathematical processing of acute period data made it possible to predict such a parameter as the preservation of working capacity in young adults in the period of residual effects of ischemic stroke (specificity was 94.4 %), while, focusing on the sensitivity of the method (33.9 %), it is not possible to reliably predict disability in ischemic stroke.

Assessing the severity of the patient's condition using the Rankin scale is the most universal and generally accepted indicator that allows for an integrated characterization of the patient's condition at any stage after stroke, including the period of residual effects.

We conducted a mathematical analysis of the relationship between the Rankin scale score in the acute period of the disease and various aspects of prognosis in the long-term period of ischemic stroke. This was demonstrated in the above-described attempt to predict the remote consequences of ischemic stroke (disability) based on available anamnesis information, the course of the acute period of the disease, and clinical and laboratory data.

The registration of a combination of 3 or more scores on the Rankin scale and simultaneously 8 or more scores on the NIHSS scale in a patient in the acute period had a high prognostic potential in relation to an unfavorable outcome of ischemic stroke, assessed on the Rankin scale as 3 scores or more (OR = 17.5; CI 95 % 1.67–182.93; $p = 0.017$).

When assessing the risk of disability in the outcome of ischemic stroke in young patients, based only on the score of 3 points or more on the Rankin scale in the acute period of the disease, its prognostic value was also demonstrated (OR = 2.66; CI 95 % 1.13–4.32; $p = 0.0089$).

At the same time, another traditional indicator for assessing the severity of stroke – NIHSS – in isolation also had a reliable effect on the chance of developing disability as a result of the disease (OR = 5.76; CI 95 % 1.12–8.07; $p = 0.0001$).

It is known that the degree of loss of ability to work and independence in everyday life, assessed by the Rankin scale, does not always strictly correlate with the presence and degree of disability. In this regard, we decided to evaluate the prognostic significance of the Rankin scale in the dynamics of the disease.

It was shown that the presence of 3 scores or more on the Rankin scale in the acute period increases the chance of main-

taining a high score (3 or more) in the period of long-term effects (OR = 2.71; CI 95 % 1.95–3.95; $p = 0.0001$).

8 scores or more on the NIHSS scale in the acute period had the same prognostic value of high Rankin scale scores in the outcome (3 scores or more) (OR = 4.83; CI 95 % 1.97–6.37; $p = 0.0001$).

We also attempted to predict the outcome of ischemic stroke at a young age using the Rankin scale, taking into account the course of the acute period of the disease. The analysis included 14 parameters characterizing the anamnesis, clinical picture and laboratory data of the acute period of stroke: gender, age, Rankin scale score in the acute period upon admission, NIHSS score, the presence of an infarction focus according to CT (MRI) results in the acute period, the involved vascular pool, ultrasound data of the brachiocephalic arteries (percentage of stenosis), lateralization of clinical symptoms in the acute period, glucose, fibrinogen, platelets levels in the acute period, significant changes in the ECG, the pathogenetic type of stroke according to the TOAST criteria and the fact of smoking.

The problem was solved by the mathematical method of discriminant analysis using the Statistica 10.0 program and included the selection of prognostically significant features that definitely differ in patients at an atypical age, who survived and formed or did not form an outcome according to the Rankin scale of 0–2 scores versus 3–5 scores after the end of the disease recovery period.

If, as a result of substituting the data of a specific patient into the decision rule, the IPI value is less than 0, then the patient is assigned to the first group (according to 0–2 Rankin scores), if the IPI is greater than 0, then to the group that formed 3–5 Rankin scores.

Based on the available data, an integrative prognostic index (IPI, Z) was formed using logistic regression by the formula:

$$Z = b_0 + b3Var3,$$

where b_0 – 4.765466; $b3$ 1.023786; $Var3$ – Rankin scale score on admission to hospital in the acute period.

Mathematical processing of the acute period data did not show any significance for predicting the acute period parameters taken into account in the analysis, except for the Rankin scale score in the acute period. The ability to predict such a parameter as good recovery and a high level of self-care (0–2 Rankin scores) in young adults in the period of residual effects of ischemic stroke (specificity 95.2 %), with the impossibility of reliably predicting more severe outcomes according to the Rankin scale (3–5 scores) the sensitivity of the method was determined as 45.8 %.

We also attempted to predict a very good (so-called excellent) outcome of ischemic stroke at a young age according to the Rankin scale (0–1 scores) according to the parameters of the Rankin and NIHSS scales in the acute period of ischemic stroke.

If, as a result of substituting the data of a specific patient into the decision rule, the IPI value is less than 0, then the patient is assigned to the group of excellent outcomes (0–1 Rankin scores), if the IPI is greater

than 0, then to the group that formed 2 or more Rankin scores in the outcome period.

Based on the available data, an integrative prognostic index (IPI, *Z*) was formed using logistic regression by the formula:

$$Z = b_0 + b3Var3,$$

where b_0 – 3.688542; *b*3 1.011257; *Var*3 – Rankin scale score on admission to hospital in the acute period.

The ability to predict such a parameter as excellent recovery and a high level of self-care (0–1 Rankin scores) in young adults in the period of residual effects of ischemic stroke was demonstrated by specificity of 79.0 %, with the impossibility of reliably predicting more severe variants of outcomes according to the Rankin scale (more than 2 scores) the sensitivity of the method was 62.1 %.

The second version of the prognostic rule, taking into account both integrative indices, showed similar results:

$$Z = b_0 + b3Var3 + b8Var8,$$

where b_0 – 3.129286; *b*3 0.5767037; b8 0.1168231; *Var*3 – Rankin scale score on admission to hospital in the acute period; *Var*8 – NIHSS score on admission to hospital in the acute period.

The ability to predict such a parameter as excellent recovery and a high level of self-care (0–1 Rankin scores) in young adults in the period of residual effects of ischemic stroke based on the Rankin and NIHSS scales in the acute period demonstrated a specificity of 85.7 %, with the impossibility of reliably predicting more severe variants of outcomes according to the Rankin scale (more than 2 scores) the sensitivity of the method was 54.5 %.

In order to clarify the role of various indicators of the patient's condition with ischemic stroke in the acute period and the possibility of predicting outcome options using them in the long-term period, we applied the decision trees method. This method took into account both discrete and continuous values for variables denoting factors of the acute period of ischemic stroke.

In total, 14 parameters characterizing the anamnesis, clinical picture and laboratory data of the acute period of stroke were taken into analysis by this machine learning method. An attempt to build a forecast using a decision tree also showed the prognostic value of integrative assessments of patients' condition using the Rankin and NIHSS scales in the acute period of the disease (Figure).

It was shown that the first decision boundary was the NIHSS score of 6.5. The NIHSS score above 6.5 was the condition for moving to the right side of the tree. The second decision boundary was the Rankin scale score in the acute period of ischemic stroke, equal to 3.5. The attempt was successful in terms of specificity (83.2 %) and quite successful in terms of sensitivity (66.1 %). Thus, using another mathematical method of data processing, the prognostic value of only integrative indicators of the patient's condition, assessed by the Rankin and NIHSS scales, was demonstrated once again.

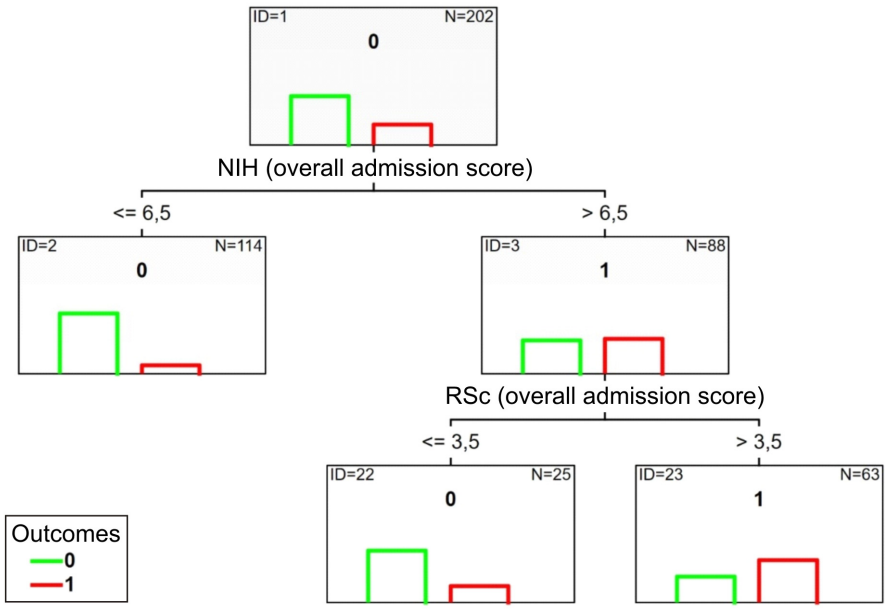

Fig. Decision tree for predicting the preservation of working capacity in the long-term period of IS in young patients: N is the number of patients, ID is the unique identifier of the tree node, NIH is the NIHSS score, RSc is the Rankin scale score in patients in the acute period

Thus, over the observation period (2–11 years), the recurrence rate was 18.3 % (n = 47), fatal outcomes were recorded in 23 young patients, disability was established in 23.4 % (n = 60), which characterizes ischemic stroke at a young age as a significant medical and social problem.

It is not possible to reliably predict disability as a result of ischemic stroke (specificity – 94.4 %, sensitivity – 33.9 %). At the same time, it remains possible to predict favorable outcomes, namely the absence of disability and the preservation of working capacity.

The study found that the Rankin and NIHSS scales have a significant prognostic value for the rate of recovery to mild and moderate status (specificity – 85.7 %, sensitivity of the method – 54.5 %). We also showed that the assessment of the patient's condition according to the NIHSS and Rankin scales in the acute period of ischemic stroke has a high prognostic value (OR 2.66–5.76) in relation to the formation of disability in the period of remote consequences.

Conclusions

The remote outcomes of ischemic stroke developed in young patients were analyzed. High prognostic value of integrative indicators of the patients' condition, assessed by the Rankin and NIHSS scales, was established. Using mathematical methods, a number of prognostic rules were identified for young patients who suffered an ischemic stroke, in terms of the absence of disability and a high level of self-care in the period of remote consequences.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 12/04/2023
Revised version received: 12/11/2023
Accepted: 03/15/2024

Please cite this article in English as: Gusev V.V., Lvova O.A., Kovtun O.P., Shamalov N.A., Sergeev A.P., Sergeeva M.V., Medvedeva D.A. The options for prognosis of the outcome of ischemic stroke in young patients. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 87-95. DOI: 10.17816/pmj41287-95

Scientific Article
UDC 616.31-08-039.71
DOI: 10.17816/pmj41296-103

ASSESSMENT OF DENTAL MOBILITY IN ELDERLY AND SENILE PATIENTS WITH VARIOUS TYPES OF DENTITION DEFECTS

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ОЦЕНКА ПОДВИЖНОСТИ ЗУБОВ У ПАЦИЕНТОВ ПОЖИЛОГО И СТАРЧЕСКОГО ВОЗРАСТА С РАЗЛИЧНЫМ ТИПОМ ДЕФЕКТОВ ЗУБНЫХ РЯДОВ

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Objective. To determine the differences in the degree of tooth mobility in elderly patients with various types of dentition defects. To establish and differentiate the degree of tooth mobility in relation to the type of dentition defect in elderly and senile patients.
Materials and methods. 500 patients aged 60 to 75 divided into 4 groups were examined. In the first group of patients, terminal defects were revealed (on one or both sides). The second group consisted of patients with included defects (on one or both sides). The third group was presented by combined defects (included and not included). Patients with single standing teeth constituted the fourth group. Patients with complete absence of teeth were excluded from the study. The assessment of dental mobility was carried out using the Periodotest device. All studies on dental mobility were conducted as part of the initial examination of the patient. To obtain objective data, periotestometry was performed 2 times in each patient. Average periotestometry data were calculated for each patient. The average readings of periotestometry for different groups of patients were determined.
Results. On the basis of the data obtained while comparing the results of periotestometry, in relation to the type of dentition defect, statistically significant differences were established ($p < 0.001$) (method used: the Kraskel – Wallis criteria). The results of periotestometry obtained in patients of group 4 were significantly higher than in representatives of other examined groups. The least mobility according to the results of periotestometry was observed in groups 2 and 3.
Conclusions. The study revealed significant differences in the degree of tooth mobility in relation to the type of dentition defect. In patients with single standing teeth, 2–3 degree of their mobility was determined, while patients with included defects had 1–2 degree of the mobility of existing teeth. The obtained data of periotestometry indicate the need to use unloading dentures in elderly patients, in order to preserve the remaining teeth in patients with single-standing teeth, as well as in patients with terminal defects of the dentition.
Keywords. Geriatric dentistry, dentition defects, tooth mobility, dental prosthetics.

Цель. Выявить различия в степени подвижности зубов у пациентов пожилого возраста с различными типами дефектов зубных рядов. Установить и дифференцировать степень подвижности зубов в зависимости от типа дефекта зубного ряда у пациентов пожилого и старческого возраста.
Материалы и методы. Обследовали 500 пациентов в возрасте от 60 до 75 лет, которых разделили на четыре группы. В первой группе пациентов представлены концевые дефекты (с одной или двух сторон). Вторая группа была представлена пациентами с включенными дефектами (с одной или двух сторон). В третьей группе – сочетанные дефекты (включенные и не включенные). Четвертая группа – это пациенты с одиночно стоящими зубами. Полное отсутствие зубов являлось критерием исключения из исследования. Оценку подвижности зубов проводили при помощи аппарата Periotest. Все исследования по подвижности зубов осуществляли в рамках первичного осмотра пациента. Для объективизации данных периотестометрию проводили 2 раза у одного и того же пациента. Каждому пациенту были рассчитаны средние данные периотестометрии. Были определены средние показатели периотестометрии для разных групп пациентов.
Результаты. Исходя из полученных данных при сопоставлении результатов периотестометрии в зависимости от типа дефекта зубного ряда, были установлены статистически значимые различия ($p < 0{,}001$) (используемый метод: критерий Краскела – Уоллиса). Результаты периотестометрии, полученные у пациентов группы 4, оказались значительно выше, чем у представителей других обследованных групп. Наименьшая подвижность по результатам периотестометрии наблюдалась в группах 2 и 3.
Выводы. В ходе исследования были выявлены достоверные различия в степени подвижности зубов в зависимости от типа дефекта зубного ряда. Выявлено, что у пациентов с одиночно стоящими зубами определяется 2–3-я степень их подвижности, в то время как у пациентов с включенными дефектами подвижность имеющихся зубов соответствует 1–2-й степени. Полученные показатели периотестометрии указывают на необходимость использования разгружающих зубных протезов у пациентов пожилого возраста с целью сохранения оставшихся зубов при одиночно стоящих зубах, а также у пациентов с концевыми дефектами зубного ряда.
Ключевые слова. Гериатрическая стоматология, дефекты зубных рядов, подвижность зубов, зубное протезирование.

INTRODUCTION

Currently, the issue of analyzing the effectiveness and restoration of chewing ability does not lose its relevance. The development of various methods, as well as the success of their clinical implementation, do not allow us to make an unambiguous conclusion about the choice of the "ideal approach" to occlusal rehabilitation of dental patients. According to the latest studies by the World Health Organization (WHO), the number of elderly and senile people is growing. Now it is more than 40 % of the population in a number of developed countries. Diseases in the elderly are expressed in non-specific manifestations of illnesses. They are characterized by multiple lesions, unpredictability of their course, frequent complications, which, in turn, leads to an extension of the rehabilitation period [1–3].

Dental health of elderly and senile people is determined by basic criteria, such as maintaining the function of existing teeth and restoring or maintaining the chewing ability with the help of various orthopedic structures [4–6].

Along with the development of modern methods of dental orthopedic rehabilitation of patients, it is necessary to strive for the widespread implementation of an objective, comprehensive approach that allows taking into account the developed joint, muscle and occlusal pathology of patients during the treatment process [7; 8].

According to numerous studies, the unsatisfactory condition of the oral cavity is determined in elderly and senile patients. Tooth loss, dentition defects, and impaired chewing ability occupy one of the leading places among the pathological processes occurring in the oral cavity [8; 10].

Dental specialists pursue the goal of delaying expensive, and in some situations traumatic rehabilitation using dental implants with the tactics of preserving teeth, prolonging the functioning of patient's teeth, including as supports when using various removable and non-removable orthopedic structures, increasing the level of comfort during treatment [11–13].

Conducting a full-fledged diagnosis, allowing for strict differentiation and development of an adequate approach to the implementation of full orthopedic rehabilitation in a patient, makes it possible to prevent not only the development of complications of dental prosthetics, but also indirectly prevent the disruption of innervation and blood supply to the maxillofacial region [14–16].

One of the most important characteristics of a tooth that affects the prognosis of treatment is its mobility. Currently, there are not enough studies that fully cover this issue.

The objective of the study is to determine the differences in the degree of tooth mobility in elderly patients with various types of dentition defects, to establish and differentiate the degree of tooth mobility in relation to the type of dentition defect in elderly and senile patients.

MATERIALS AND METHODS

The study was conducted at the Department of Propaedeutics of Dental Diseases of the E.V. Borovsky Institute of Dentistry, Sechenov University. The study was carried out in accordance with the basic bioethical standards of the Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research, as amended (2000, as amended in 2008), the Universal Declaration on Bioethics and Human Rights (1997), and the Council of Europe Convention on Human Rights and Biomedicine (1997). The study was approved by the local ethics committee (protocol No. 30–20 dated October 21, 2020). Each patient signed a voluntary informed consent. The study was conducted during the comprehensive rehabilitation of dental patients of this group with various types of partial secondary edentia.

A total of 500 participated in the study. They were divided into 4 groups of 125 people each. In the first group of patients, terminal defects were revealed (on one or both sides). The second group consisted of patients with included defects (on one or both sides). The third group was presented by combined defects (terminal and included). Patients with single standing teeth constituted the fourth group. Patients with complete absence of teeth were excluded from the study.

Attention was paid to the presence / absence, and if present – to the type of orthopedic structure, the frequency of use of certain orthopedic structures (partial removable plate dentures, clasp dentures), the age of their manufacture and installation.

Research in the clinic was carried out using the Periotest device, registered under number 2006/2534 on December 28, 2006). The device is designed to study the ability of the periodontium to return the tooth to its original position after the application of external forces[1].

The Periotest device is equipped with an electronic analyzer and an intraoral sensor with a striker based on the wire connection principle. Data is obtained as follows. The electronic analyzer generates a pulse transmitted to the striker at a frequency of 4 strikes per second. For one measurement, 16 pulses are used. The force of the device is safe for hard and soft tissues of the maxillofacial region, including the periodontium. The place of application of force is the zone between the contour height and the occlusal part of the tooth. The sensor, striker and electronic analyzer take the percussion impact on the tooth based on 16 impacts, which are taken into account as averaged. The electronic analyzer is responsible for the accuracy of the required indicators read during the application of each 16 pulses, displayed by the PT index. The Periotest S user manual provides a gradation of the mobility of the object under study from -8

[1] Periotest Classic, available at: http://www.med-gulden.com/downloads/02_english/02_Operating%20Manual/Periotest_Classic.pdf

to +50. The interpretation of the obtained periostemetry data was made according to the scale:

- –8 – +9 – the tooth is immobile (physiological mobility);
- +10 – +19 – 1st degree mobility;
- +20 – +29 – 2nd degree mobility;
- +30 – +50 – 3rd degree mobility.

In repeated studies, the same impact zone of the examined tooth and the same vector of force application to the tooth were used to obtain objective data. All studies on dental mobility were conducted as part of the initial examination of the patient. To obtain objective data, periotestometry was performed 2 times in each patient. A total of 500 manipulations were performed. Average PT data were calculated for each patient. Average PT values were determined for different groups of patients.

Statistical analysis was performed using the StatTech v. 3.1.10 program (developed by StatTech LLC, Russia). Quantitative indicators were assessed for compliance with the normal distribution using the Kolmogorov-Smirnov criterion. In the absence of a normal distribution, quantitative data were described using the median (*Me*) and the lower and upper quartiles ($Q_1 - Q_3$). Comparison of three or more groups by a quantitative indicator whose distribution differed from normal was performed using the Kruskal-Wallis test, and post hoc comparisons were performed using the Dunn test with Holm's correction.

RESULTS AND DISCUSSION

Based on the obtained data, when comparing the results of periotestometry depending on the type of dentition defect, statistically significant differences were established ($p < 0.001$) (the method used: Kruskal-Wallis criterion).

The obtained data (table) show greater stability of the periotestometry results in the 2nd and 3rd study groups than in the 1st one. This can be explained by the most uniform distribution of the occlusal load in the 3rd study group, which is confirmed by the results of occlusiography and myography of the masticatory muscles. It should be taken into account that the manifestations of age-related changes in periodontal tissues negatively affect the degree of the natural teeth stability. This emphasizes the need to use implant-based orthopedic structures in elderly patients. Due to the ability to compensate for the occlusal load without using natural teeth, it became possible to stabilize natural teeth. In the 4th study group, the periotestometry indicators are significantly higher than in the first three study groups. This is explained by the fact that single teeth do not have the ability to compensate for the chewing load imposed on them, which is aggravated by the lack of approximal contacts and additional vertical loads affecting the tooth.

When comparing the obtained results with previously published studies, it can be noted that there are no publications in domestic and foreign literature devoted to the

Periotestometry results in the study groups

Parameter	Category	Periotestometry result			*p*
		Me	$Q_1 - Q_3$	*n*	
Type of dentition defect	Group 1 (terminal defects (on one or both sides))	25	17–29	125	$p_{1-4} < 0.001$ $p_{2-4} = 0.003$ $p_{3-4} < 0.001$
	Group 2 (included defects (on one or both sides))	26	17–29	125	
	Group 3 (combined defects)	26	17–29	125	
	Group 4 (single standing teeth)	29	25–34	125	

Note: * – the differences in the indicators are statistically significant ($p < 0.05$).

problem of tooth mobility in patients with various dentition defects. Studies of tooth mobility were mainly conducted in patients with various types of periodontal pathologies [12; 15].

The studies note the relationship between alveolar bone resorption and the degree of tooth mobility, which indirectly corresponds to the results we obtained, since elderly and senile patients undoubtedly have bone tissue lysis, especially in the area of teeth located next to dentition defects [9]. A number of foreign publications note a relationship between tooth mobility and changes in the hormonal background of patients [17; 18], for example, during pregnancy or during the menstrual cycle, however, these articles studied patients with intact dentition and a younger age, and this information cannot be unambiguously applied to the patients in our study [19; 20].

Conclusions

The study revealed significant differences in the degree of tooth mobility in relation to the type of dentition defect. In patients with single standing teeth, 2–3 degree of their mobility was determined, while patients with included defects had 1–2 degree of the mobility of existing teeth. The obtained data of periotestometry indicate the need to use unloading dentures in elderly and senile patients, in order to preserve the remaining teeth in patients with single-standing teeth, as well as in patients with terminal defects of the dentition.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

Dorofeev A.E. – collection and processing of materials, data analysis.

Sevbitov A.V. – concept and design of the study.

Utyuzh A.S. – data analysis.

Mironov S.N. – collection and processing of materials, writing the text.

Emelina E.S. – literature review, writing the text.

Kuznetsova M.Yu. – data analysis, statistical processing of data.

Received: 11/07/2023
Revised version received: 12/15/2023
Accepted: 03/15/2024

Please cite this article in English as: Dorofeev A.E., Sevbitov A.V., Utyuzh A.S., Mironov S.N., Emelina E.S., Kuznetsova M.Yu. Assessment of dental mobility in elderly and senile patients with various types of dentition defects. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 96-103. DOI: 10.17816/pmj41296-103

PREVENTIVE AND SOCIAL MEDICINE

Scientific Article
UDC 316.615.618
DOI: 10.17816/pmj412104-111

IMMUNOMODULATORY THERAPY OF PRECANCERS OF THE CERVIX – OPINION OF MEDICAL PROFESSIONALS AND STUDENTS

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ИММУНОМОДУЛИРУЮЩАЯ ТЕРАПИЯ ПРЕДРАКОВЫХ ЗАБОЛЕВАНИЙ ШЕЙКИ МАТКИ – МНЕНИЕ МЕДИЦИНСКИХ РАБОТНИКОВ И СТУДЕНТОВ

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Objective. To assess the relevance of immunomodulatory therapy of precancerous diseases of the cervix among medical professionals and students. Precancerous diseases of the cervix combine pathological processes characterized by the structural changes in the epithelium of the cervix. If not treated, they lead to the development of cervical cancer. At present there are no selective drugs for the human papillomavirus. To administer immunotropic medicines it is necessary to know the mechanism of effect on the immune system.
Materials and methods. The study was conducted using an anonymous online questionnaire on the Google Forms platform (https://vk.com/away.php?utf=1&to=https%3A%2F%2Fforms.gle%2FRtT7PktnCrLqBB1x8). The

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questionnaire is presented as part of a one-stage (cross-sectional) study. Data analysis was carried out using Microsoft Excel 2010 graphs and tables. Empirical, sociological and statistical research methods were used. The indicators of the structure of the respondents were calculated, the reliability of the differences was determined by the Student's *t*-criterion, confidence differences were considered at significance of $p < 0.05$.

Results. The average age of the respondents was 30.4 ± 10.8 years. 46 people (75.4 %) are aware of the possibility of using immunomodulation as therapy for precancerous diseases of the cervix, and 15 people (24.6 %) are not aware of it. 41 respondents (67.2 %) would administer the therapy themselves and their close people; 12 people (19.7 %) find it difficult to answer; 8 respondents (13.1 %) do not agree to administer the therapy.

Conclusions. Medical students have an idea about immunomodulatory therapy in gynecology in 55.9 % of cases. Doctors of different specialties in 100 % of cases are aware of the treatment, see the benefits of prescribing drugs. Students` awareness of the possibilities of immunomodulatory therapy is sufficient, they get additional knowledge from clinical recommendations on the specialty in the practical course.

Keywords. Precancer of cervix, human papilloma virus, papilloma-viral infection, cervical intraepithelial neoplasia (CIN).

Цель. Оценка актуальности использования иммуномодулирующей терапии предраковых заболеваний шейки матки среди медицинских работников и студентов. Предраковые заболевания шейки матки объединяют патологические процессы, характеризующиеся наличием структурных изменений эпителия шейки матки. Без лечения приводят к развитию рака шейки матки. Сегодня нет препаратов, избирательно действующих на вирус папилломы человека. Назначение иммунотропных препаратов требует знаний механизма действия на иммунную систему.

Материалы и методы. Исследование проводилось при помощи анонимного онлайн-анкетирования с помощью Google-формы (https://vk.com/away.php?utf=1&to=https%3A%2F%2Fforms.gle%2FRtT7PktnCrLqBB1x8). Анкета представлена в рамках одномоментного (кросс-секционного) исследования. Анализ данных проводился с использованием графиков и таблиц Microsoft Excel (2010). Оценка распределения признаков на нормальность проводилась с помощью критерия Шапиро – Уилка. Использованы эмпирический, социологический и статистический методы исследования. Рассчитаны показатели структуры опрошенных, достоверность различий определена *t*-критерием Стьюдента, доверительные различия считались при пороге значимости $p < 0,05$.

Результаты. Средний возраст опрошенных составил 30,4 ± 10,8 г. Ознакомлены с возможностью применения иммуномодуляции в качестве терапии предраковых заболеваний шейки матки 46 человек (75,4 %), и не знакомы – 15 (24,6 %). Назначили бы себе и своим близким – 41 человек (67,2 %); 12 (19,7 %) – затрудняются ответить; нет, не согласны назначить – 8 (13,1 %).

Выводы. Студенты медицинского вуза имеют представление об иммуномодулирующей терапии в гинекологии в 55,9 % случаев. Врачи разных специальностей в 100 % случаев знакомы с лечением, видят пользу в назначении препаратов. Информированность о возможностях иммуномодулирующей терапии обучающихся в вузе достаточная, дополнительные знания они получают в процессе практической деятельности из клинических рекомендаций по специальности.

Ключевые слова. Предрак шейки матки, вирус папилломы человека, папилломавирусная инфекция, цервикальные интраэпителиальные неоплазии (CIN).

INTRODUCTION

The concept of “precancerous diseases of the cervix” first occurred in the last century [1]. These are pathological conditions manifested by the presence of structural changes in the epithelium of the cervix. Without treatment, cervical cancer may develop [2], but there is some positive aspect to the problem – the development of the disease takes from 3 to 8 years [3; 4]. To date, the statistics for the Russian Federation are disappointing: 15.1 cases per 100 thousand population. The incidence of

precancerous pathology is steadily increasing [5; 6]. A preventive measure for cervical cancer is the timely detection and treatment of background and precancerous conditions [7].

Non-specific antiviral, restorative therapy, desensitizing agents, tranquilizers, interferon preparations and their inducers, ozone therapy, adaptogens, synthetic immunomodulators are often prescribed additionally [8; 9]. It would seem prudent to determine the role of immunotropic therapy in the complex treatment of precancerous pathology of the cervix [10; 11].

The objective of the study was to assess the relevance of the use of immunomodulatory therapy for precancerous diseases of the cervix among medical professionals and students.

MATERIALS AND METHODS

61 people were interviewed using an anonymous online survey, conducted on the Google Forms platform. The sample size was not calculated beforehand. The questionnaire was presented as part of a one-stage (cross-sectional) study, which included the collection of information and analysis of data at a certain point in time.

Two groups were selected for comparative analysis: Group 1 comprised 34 people, and Group 2 – 27 people.

The data analysis was conducted using Microsoft Excel graphs and tables (version 2010). The age of the respondents was calculated using formulas for determining the average value and standard deviation. The assessment of the distribution of signs for normality was carried out using the Shapiro–Wilk test. The distribution was normal. The results were presented in figures and tables with conclusions.

Empirical, sociological and statistical research methods were used. Indicators of the structure of respondents were calculated. Reliability of differences was determined using the Student's t-test. Confidence intervals were considered at a significance level of $p < 0.05$, i.e. the confidence level for the data is 95 %.

RESULTS AND DISCUSSION

The average age of the respondents was 30.4 ± 10.8 years, the vast majority of respondents were 23 years old, the minimum age was 22 years, the maximum age was 55 years.

First, the authors determined the general attitude towards immunomodulatory therapy in gynecology among practitioners and students. It was found that 46 people (75.4 %) were aware of the possibility of using immunomodulation as therapy for precancerous diseases of the cervix; 15 people (24.6 %) were not aware of it; 47 people (77.0 %) saw benefits in treating precancerous cervical diseases associated with HPV and supported this approach, while 14 people (23.0 %) had a different opinion; almost half of the doctors – 27 respondents (44.3 %) – used these drugs in addition to treatment for cervical dysplasia (associated

with HPV), in particular, 20 of them (32.8 %) did it after surgical manipulations on the cervix. 37 people (60.7 %) justified the use of immunomodulators based on clinical recommendations; 8 respondents (13.1 %) rely on books on obstetrics, gynecology, immunology, and oncology; the other 8 (13,1 %) follow articles in medical journals; 5 (8,2 %) respondents rely on their colleagues and acquaintances; the remaining 3 (4,9 %) people responded that they didn't prescribe these medications at all.

Specialists were also asked if their patients were satisfied with taking immunomodulatory drugs. 27 (44.3 %) respondents said that their patients were satisfied, 23 (37.7 %) people had no experience with immunomodulatory drugs, 8 (13.1 %) people did not use this kind of drugs, and 3 (4.9 %) respondents stated that their patients were not satisfied with taking immunomodulatory drugs.

Indications for the use of immunomodulatory therapy included: cervical dysplasia, according to 31 people (50.8 %); no such diseases – 15 respondents (24.6 %); acceleration of recovery after surgical treatment – 6 respondents (9.8 %); after an unsuccessful in vitro fertilization attempt – 4 (7.3 %); miscarriage – one person (1.2 %); chronic endometritis – one person (1.3 %); cervicitis and vaginitis – 3 respondents (5 %).

Five of the surveyed doctors (8.2 %) claimed that their patients experienced side effects from therapy; 24 respondents (39.3 %) reported no side effects in their patients; and 32 people (52.5 %) have no personal experience with immunomodulators.

In general, the attitudes towards immunomodulatory therapy are shown in the figure: 21 people (34.4 %) find it acceptable to use, 17 respondents (27.9 %) consider it possible, 15 people (24.6 %) think it is safe to use, 5 people (8.2 %) see it as unsafe, and 3 people find it completely unacceptable (4.9 %).

When conducting a comparative analysis of the responses of doctors and students, the authors found no significant differences in the following parameters: familiarity with immunomodulatory therapy; reliance on books on obstetrics and gynecology and scientific articles when prescribing this type of therapy by doctors; opinion that immunomodulatory therapy is safe and/or completely unacceptable (table).

Drawing an analogy to the above conclusion, we have characterized all other sample indicators in accordingly.

Statistically significant differences were obtained in the answers to the questions about the use of immunomodulatory drugs, planning to use them; their use in combination with CIN therapy; the presence of side effects; reference to the opinions of colleagues and clinical recommendations as well as medical journals when prescribing these drugs; attitude to immunomodulatory therapy as safe; the possibility of self-prescription of treatment and/or prescribing it to relatives; refusal to prescribe such treatment.

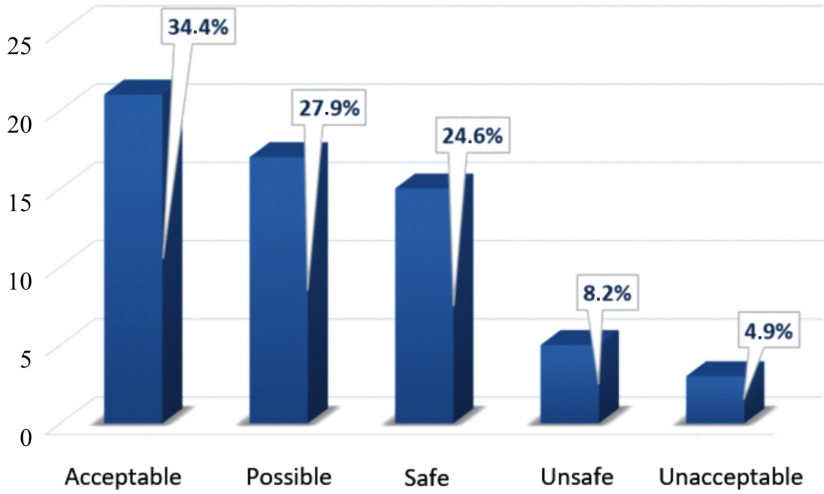

Fig. Attitude of the respondents to immunomodulatory therapy

Attitude of the respondents in the study groups to immunomodulatory therapy

Parameter	Group 1 ($n = 34$), %	Group 2 ($n = 27$), %	Reliability of differences, R
Respondent is familiar with immunomodulatory therapy	55.9	100	0.2
Respondent sees benefit from immunomodulatory therapy	58.8	100	0.01
Respondent uses of immunomodulatory drugs in practice	0	77.8	0.01
Respondent is planning to use immunomodulatory drugs	64.7	0	0.01
Respondent uses immunomodulators in therapy (besides CIN)	0	100	0.0001
Respondent registered side effects of immunomodulators	70.6	0	0.01
Respondent refers to clinical guidelines when administering immunomodulators	29.4	100	0.01
Respondent refers to books on obstetrics and gynecology when administering therapy	11.7	14.8	0.5
Respondent refers to the opinion of colleagues in the therapy	23.5	0	0.003
Respondent refers to scientific articles when administering therapy	17.6	7.4	0.2
Respondent refers to the medical journals in the appointment of therapy	23.5	0	0.003
Respondent considers therapy with immunomodulators as safe	79.4	100	0.001
Respondent is satisfied with the price of immunomodulatory drugs	0	100	0.0001
Respondent is not satisfied with the price of immunomodulatory drugs	26.5	0	0.002
Respondent finds it difficult to give an answer on the price of immunomodulatory drugs	73.5	0	0.01
Respondent would prescribe immunomodulatory treatment to themselves and/or their family	41.2	100	0.002

End of the Table

Parameter	Group 1 ($n = 34$), %	Group 2 ($n = 27$), %	Reliability of differences, R
Respondent would not prescribe immunomodulatory therapy to anyone	23.5	0	0.003
Respondent considers therapy with immunomodulators acceptable	23.5	48.1	0.05
Respondent considers therapy with immunomodulators possible	50	0	0.05
Respondent considers therapy with immunomodulators safe	2.9	51.9	0.15
Respondent considers therapy with immunomodulators unsafe	14.7	0	0.02
Respondent considers therapy with immunomodulators totally unacceptable	8.8	0	0.08

This study showed a high level of awareness of immunomodulatory therapy among the medical community – 75.4 % ($n = 46$). This confirms information from Russian publications on the commitment of physicians to this type of treatment [8;9].

Modern Russian clinical guidelines recommend the use of immunological drugs for the treatment of precancerous cervical diseases only in the presence of human papillomavirus, in addition to excisional treatment methods. In the study, 77 % of medical professionals believed that this type of therapy was effective against human papilloma virus (confirming information in clinical recommendations), while 23 % believed it was ineffective. At the same time, 34.4 % ($n = 21$) actively used these drugs to treat HPV infections, while 29.5 % ($n = 18$) did not consider them effective presumably based on literature reports about the lack of evidence supporting their effectiveness against HPV [10].

According to the respondents, 44.3 % ($n = 27$) often use immunomodulators in the treatment of gynecological pathology unrelated to cervical dysplasia – miscarriages, unsuccessful IVF attempts, chronic endometritis, etc. This helps preserve the reproductive health of women, as this issue is considered a strategic one for healthcare in many official statistics.

Doctors who perform surgical procedures on the cervix often prescribe immunomodulators to help promote tissue healing after surgery and provide complex treatment for human papillomavirus. 66.7 % of them recommend using immunomodulators, while 33.3 % do not. Medical literature has shown that vaccination and proper treatment for precancerous conditions can be effective in preventing cervical cancer [7–10].

It was gratifying to learn that medical professionals adhered to clinical guidelines (60.7 %), as well as books and journals in their field, thereby enhancing their expertise.

When comparing the two groups, we found a generally favorable attitude towards the administration of immunomodulatory

therapy. 100 % of respondents from group 2 saw the benefit of prescribing immunomodulators, and 77.8 % used this type of therapy in practice. However, only 58.8 % of respondents in group 1 saw the benefits of prescribing it ($p = 0.01$), and did not use it in practice ($p = 0.05$).

In addition, doctors tend to recommend treatments based on clinical guidelines (100 %), while students find it acceptable to consult with their colleagues (23.5 %) and read journal articles on the subject ($p = 0.003$).

Conclusion

77 % ($n = 47$) of medical workers see benefits from the use of immunomodulatory therapy, while 34.3 % ($n = 21$) actively utilize this type of treatment in practice. Medical students have a good understanding of immunomodulation in gynecology in 55.9 % of cases. Doctors of various specialties are aware of this treatment in 100 % of the cases, they see benefits in prescribing it for their patients, as well as recommending it to relatives. Overall, medical professionals have a sufficient understanding of the potential of this therapy during their studies, and they gain additional knowledge about indications, contraindications, and potential complications through practical training, primarily through clinical guidelines.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

Lykova E.A. – collection and processing of materials, writing the text.

Rosyuk E.A. – material processing, writing the text, editing.

Received: 11/26/2023
Revised version received: 12/15/2023
Accepted: 03/15/2024

Please cite this article in English as: Lykova E.A., Rosyuk E.A. Immunomodulatory therapy of precancers of the cervix – opinion of medical professionals and students. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 104-111. DOI: 10.17816/pmj412104-111

Scientific Article
UDC 2.616-006.6-07: 316.6
DOI: 10.17816/pmj412112-122

LEVEL OF COMPETENCE OF RURAL PHYSICIANS IN PRIMARY HEALTH CARE IN THE DIAGNOSIS OF MALIGNANT NEOPLASMS OF MAIN LOCALIZATIONS

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УРОВЕНЬ КОМПЕТЕНТНОСТИ СЕЛЬСКИХ ВРАЧЕЙ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ В ВОПРОСАХ ДИАГНОСТИКИ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ ОСНОВНЫХ ЛОКАЛИЗАЦИЙ

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Objective. To analize the level of rural PHC doctors` competence on the issues of diagnosis and routing patients with suspected cancer.
Materials and methods. The study was conducted using a survey of medical workers involved in the diagnosis of malignant neoplasms of four main localizations (specialist doctors and paramedics of examination rooms) of the Central District Hospital of five rural municipal districts of the Magnitogorsk oncological cluster of Chelyabinsk region. 35 physicians took part in the study.
Results. The results of the survey were quite negative: the minority of respondents are aware of the exact duration of the mandatory initial diagnostic examination, the period of informing the oncologist about the patient diagnosed with cancer, and the scheme for assigning municipal medical organizations to outpatient oncology centers.
Conclusions. The surveyed contingent is characterized by: low oncological alertness and unsatisfactory competence concerning the initial manifestations of malignancies; inclusion of symptoms of the formed cancer in the number of early manifestations of malignancies, which means that a doctor, unsure of the diagnosis, as if waiting for the appearance of an obvious, from his point of view, symptom of a tumor, and as a result, the patient has an advanced stage of cancer; 3) flawed ideas about the full list of necessary methods for diagnosing malignant neoplasms of leading localizations; unsatisfactory knowledge of regulatory documentation on the routing of patients with suspected cancer.
Keywords. Uterine breast, lung and prostate cancer, rural health care.

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Цель. Анализ уровня компетентности сельских врачей по вопросам диагностики и маршрутизации пациентов с подозрением на злокачественные новообразования.
Материалы и методы. Исследование проведено с помощью анкетирования 35 медицинских работников (врачи-специалисты и фельдшеры смотровых кабинетов) центральных районных больниц пяти сельских муниципальных районов Магнитогорского онкологического кластера Челябинской области, участвующих в диагностике злокачественных новообразований четырёх основных локализаций.
Результаты. Анализ ответов опрошенных выдал весьма негативный результат: точную продолжительность обязательного первичного диагностического обследования, срок информирования онколога о выявленном больном со злокачественными новообразованиями и схему закрепления муниципальных медицинских организаций за центрами амбулаторной онкологии знает явное меньшинство опрошенных.
Выводы. Опрошенный контингент характеризуется: низкой онконастороженностью и неудовлетворительной компетенцией по вопросам начальных проявлений злокачественных новообразований; включением симптомов сформировавшегося рака в число ранних проявлений злокачественного новообразования, т.е. врач, не уверенный в диагнозе, ориентируется исключительно на очевидный симптом опухоли, игнорируя косвенные признаки заболевания, а в результате у пациента диагностируется запущенная стадия рака; недостаточными представлениями о полном перечне необходимых методов диагностики злокачественных новообразований ведущих локализаций; неудовлетворительными знаниями нормативной документации о маршрутизации пациентов с подозрением на злокачественное новообразование.
Ключевые слова. Рак тела матки, молочной железы, легкого и предстательной железы, сельское здравоохранение.

INTRODUCTION

According to the database from Globocan, which is generated by the International Agency for Research on Cancer and which includes primary cases of malignant neoplasms (MN) in 28 localizations from 184 countries. By 2018, the total number of MNs was more than 14 million cases with about 8 million deaths per year. Among all cases of MNs, the first place is taken by lung cancer (LC) (13.0 %) and the second place is taken by breast cancer (BC) (11.8 %) [1; 2].

There is also a steady growth of MNs in the Russian Federation. For example, the incidence rate increases by 1.5 % annually. The total mortality from oncologic tumors is on 2nd place after diseases of the circulatory system [3; 4]. The "record" on detection of new cases of MNs was updated in 2019. More than 640 thousand cases were detected, which is 2.5 % higher than the data of 2018. [5]. Since 2018, according to the data of The Moscow Research Institute named after Pyotr Alexandrovich Herzen, the main MNs in terms of detectability among women are BC (51.5 %) and uterine corpus cancer (UC) (18.9 %), among men are LC (47.6 %) and prostate cancer (PC) (41.6 %) [6].

If at the beginning of the XXI century, the incidence of PC reached 700 thous. new cases per year, the current total number of registered new cases of PC is more than one million, of which 119 thous. are registered in developing countries and 895 thous. in economically developed countries [7; 8]. The highest incidence of this type of cancer is traditionally registered in Scandinavian countries. There are 55.3–61.4 cases

per 100,000 men [9]. UC, which is the main pathology in gynecologic oncologic patients, also shows a steady increase in the number of new cases. It is almost 320 thous. per year with a mortality rate of 75 thous. cases [10; 11]. At the same time, a systematic increase in the incidence of the four leading localizations of MNs is of particular concern among the oncologists all over the world due to the high level of neglect of detected cases [5; 12].

When analyzing the reasons for the high rate of MNs neglect, the most common cause is insufficient funding. Indeed, in many territories of the country there is a deficit of financing of the "Program of state guarantees of free medical care for citizens". The total underfunding in 50 regions of the Russian Federation is almost 125 billion rubles. In addition, it is expected that the Ministry of Health will receive less in the current year than in the previous year due to a significant adjustment of the federal budget. All these factors force most regions to plan the volume of medical care based on financing rather than on the real needs of the territory's residents [13; 14] and on the material and technical equipment of diagnostic departments. Taking into account these circumstances, the main aims of primary health care (PHC) facilities are to establish a preliminary diagnosis of MNs, at the same time the competence and oncological alertness of medical personnel, as well as the optimization of exam rooms and medical check-ups are very important [15; 16].

The aim of the study is to analyze the level of competence of rural physicians in diagnosing and routing patients with suspected malignant neoplasms.

MATERIALS AND METHODS

The one-stage sociological research was conducted by surveying medical specialists and paramedics of exam rooms in the central district hospitals (CDH) of five rural municipal districts of the Magnitogorsk oncological cluster in the Chelyabinsk region.

The study was conducted between March and January 2020 on the base of CDHs of Agapovsky, Verkhneuralsky, Nagaybaksky, Bredinsky and Kizilsky rural municipal districts of the Chelyabinsk region. The actual survey was carried out during production meetings at the respondents' place of work. This stage of the research was conducted in accordance with the Federal Law of 27.07.2006 No. 152-FZ "On Personal Data".[1] Each respondent gave written permission to participate in the survey.

The inclusion criteria of the respondents were: length of service in the current occupation and employment in a rural area for more than five years.

Non-inclusion criteria: medical specialization does not involve contact with cancer patients.

The exclusion criteria are: length of service in the current occupation and

[1] On personal data: Federal Law No. 152-FZ of 27.07.2006. M. 2006; 5.

employment in a rural area for less than five years.

35 physicians participated in the study, including seven obstetrician-gynecologists, seven primary care physicians, four surgeons, four general practitioners (GPs), three urologists, seven paramedics of female exam rooms and three paramedics of male exam rooms of outpatient clinics. This means that potentially all of these health care employees could have had contact with cancer patients, which makes the current study as a cohesive study.

The study was conducted on the general total of health employees of five CDHs who have contact with cancer patients.

Statistical methods. Statistical processing of questionnaires included data grouping, database formation, construction of combination tables, calculation of extensive indicators. The measurement was done in percentages, as the main and additional targets are extensive indicators.

The conducted study complies with the standards of the Declaration of Helsinki and was approved by the Independent Ethical Committee of the Federal State Budgetary Educational Institution of Higher Education "South Ural State Medical University" of the Ministry of Health of the Russian Federation (Protocol No. 29 of 11.05.2022).

RESULTS AND DISCUSSION

The main of a whole group of factors influencing the quality of medical care are professional competence and experience of medical personnel. In the case of oncology care provided at the level of municipal rural health care, this applies to primary care physicians, general practitioners, obstetricians-gynecologists, urologists, surgeons of outpatient clinics and paramedics of male and female exam rooms.

The studied contingent of these specialists consisted of women in 65.8 %. These are all obstetricians-gynecologists, there are 85.8 % of paramedics of female exam rooms and the same number of district therapists. Men predominantly work as surgical specialists – 75.0 % of surgeons, 100 % of urologists, and 66.8 % of paramedics in male exam rooms.

20.0 % of all surveyed are retirees. The highest share is among GPs (50.1 %). Respondents under 30 years of age are only 11.5 %, there is a deficit associated with the age turnover of doctors in the surveyed rural CDHs. However, the age of health workers can only indirectly indicate about their experience; the study of length of service in the specialization is more informative for this purpose.

As shown in Table 1, the share of respondents who have experience allowing to obtain the highest qualification category or at least the first one, i.e. more than 10 years, is 85.6 %. This means that this is the majority of those surveyed, but in reality only every fifth person has the highest category – the majority of urologists (66.6 %) and paramedics of male exam rooms (33.4 %). Only every tenth respondent received the 1st qualification category. As a result, there is a significant share of those among the respondents whose

long professional experience is not characterized by an appropriate qualification assessment. In general, the length of professional experience was weakly correlated ($r = +0.24 \pm 0.008$) with the possession of qualification score among the surveyed medical workers.

As postgraduate education in various forms has an extremely positive impact on the level of professional training of medical personnel, it was obligatory to clarify the fact of professional retraining. It was determined that the vast majority of respondents (85.6 %) have improved their professional qualifications in various forms over the past five years. The share of those who did not pass it is not high, it is only 8.5 %.

They are all recent graduates of medical universities and have not yet completed their mandatory postgraduate training. As a result, only 5.9 % of respondents did not complete mandatory professional training. As oncology is compulsorily included in the programs of all professional development cycles of all specialties, it is obvious that the majority of the surveyed should have knowledge of modern diagnostics of MNs and routing of such patients. Routing of MNs patients is described in detail in the order of the Ministry of Health of the Chelyabinsk region from January 19, 2018 № 68[2] and in the order of the Ministry of Health of the Chelyabinsk region from 27.01.2020 № 65[3]. Taking into account the information contained in these documents, tests were formed to analyze the respondents' knowledge about the duration of the initial diagnostic examination, the period of informing an oncologist about a patient with MNs, and the assignment of rural CDHs to ambulatory oncological care centers (CAOPs).

The analysis of the answers of the respondents revealed an unexpected result: only a small part of the respondents know the exact duration of the mandatory primary diagnostic examination from the moment of suspicion of MNs – from 14.4 % of paramedics in female exam rooms to 50.1 % of surgeons, while primary care physicians and general practitioners have no information on these issues at all. Only two-thirds of paramedics of male exam rooms have some perceptions related to this issue.Moreover, an extremely negative situation has developed with regard to the issue of the timeframe for informing an oncologist about a detected patient with MNs. Only a few obstetrician-gynecologists and primary care physicians have knowledge of the maximum allowable time frame. This period can be in the range of up to 10 days for the majority of respondents. Respondents represent the scheme of assignment

[2] On the routing of adult patients in the provision of medical care in the profile of oncology in the Chelyabinsk region: order of the Ministry of Health of the Chelyabinsk region No. 68 from 19.01.2018. Chelyabinsk 2018; 20.

[3] Schemes of attachment of medical organizations and municipalities of the Chelyabinsk region to the Centers of outpatient oncological care: order of the Ministry of Health of the Chelyabinsk region No. 65 from 27.01.2020. Chelyabinsk 2020; 20.

Table 1

Distribution of respondents by length of professional experience, %

Health care workers	Length of work experience, in years					
	0–5	6–9	10–14	15–19	more than 20	total
GP	24.8	24.8	–	–	50.4	100
Obstetrician-gynecologists	14.5	–	–	14.5	71.0	100
Surgeons	–	–	–	24.9	75.1	100
Primary care physicians	–		29.0	–	71.0	100
Urologists	–	–	–	33.4	66.6	100
Paramedics of male exam rooms	–	–	33.7	–	66.6	100
Paramedics of female examining rooms	14.2	14.2	43.2	14.2	14.2	100

Table 2

Distribution of respondents by degree of awareness of the main sections of the orders of the Ministry of Health of the Chelyabinsk region from 19.01.2018 No. 68 and from 27.01.2020 No. 65, %

Health care workers	Provisions of the orders					
	Duration of the initial diagnostic examination		Timeframe for informing an oncologist about a detected patient with MNs		Assignment scheme to outpatient oncology centers	
	know	do not know	know	do not know	know	do not know
GP	–	100.0	–	100.0	–	100.0
Obstetrician-gynecologists	28.5	71.5	14.4	85.6	57.0	43.0
Surgeons	50.1	49.9	–	100.0	25.2	74.8
Primary care physicians	–	100	14.4	85.6	57.0	43.0
Urologists	33.4	66.6	–	100.0	66.9	33.1
Paramedics of male exam rooms	66.6	33.4	–	100.0	66.4	33.6
Paramedics of female exam rooms	14.4	85.6	–	100.0	71.7	28.3

of municipal medical organizations to outpatient oncology centers relatively well: 49.1 % of all respondents completely correctly represent it. The remaining respondents, in addition to the correct referral of the patient, may issue an erroneous referral to some regional cancer hospital.

As all medical workers of rural CDHs who could come into contact with cancer patients were familiarized "by signature" with the above orders, this level of awareness of CDH doctors should be considered unsatisfactory.

Despite the necessity of knowledge of normative documentation concerning the routing of patients with MNs, the level of competence of medical personnel in the symptoms of MNs and methods of their di-

agnosis remains the main issue in the study of the causes of neglect of MNs of the leading localizations. Primary care physicians, GPs, surgeons and paramedics of male exam rooms are involved in diagnosing LC in CDHs in rural areas. The analysis of their competence in the clinical picture and in the obligatory methods of LC diagnosis revealed a number of very negative facts (Table 3): the knowledge of early symptoms of central LC is correctly formed in a clear minority of primary care physicians (14.4 %) and only every fourth surgeon and one third of paramedics of male exam rooms. Only among GPs, three out of four specialists correctly identify the symptomatology of central LC. It should be noted that one third of respondents from among those who have insufficient knowledge of early symptomatology of central LC mention symptoms of later stages of the disease in addition to early symptoms.

The situation with respondents' competence in the clinical symptomatology of peripheral LC is similarly bad. Thus, only half of surgeons, a quarter of GPs and 28.8 % of primary care physicians have a good knowledge in this question. There is no one among paramedics of male exam rooms who knows the symptomatology of peripheral LC. All surgeons, three out of four primary care physicians, half of GPs and every third paramedic of male exam rooms fully know the mandatory list of diagnostic methods for central LC.

Surgeons, GPs, obstetrician-gynecologists and paramedics of female exam rooms are involved in the diagnosis of breast cancer in rural areas. An analysis of their competence in the clinical picture and diagnostic methods of breast cancer revealed an equally dismal situation as in LC (Table 4). Thus, only 85.50 % of obstetrician-gynecologists, 57.4 % of paramedics of female exam rooms, half of surgeons and a quarter of GPs are correctly informed about the early symptoms of breast cancer. Moreover, four out of five respondents, who have insufficient knowledge of the clinical picture of the early stages of breast cancer, cite both the early and late symptoms of breast cancer at the same time.

Table 3

Share of respondents with correct understanding of the clinical picture and methods of diagnosing LC, %

Health care LC workers	Awareness of clinical picture and diagnostic methods					
	Early symptomatic of central LC		The difference in the clinical picture of central LC from peripheral LC		Methods LC diagnostics	
	know	do not know	know	do not know	know	do not know
GP	75.0	25.0	25.0	75.0	50.0	50.0
Surgeons	25.0	75.0	50.0	50.0	100.0	–
Primary care physicians	14.4	85.6	28.8	71.2	71.4	28.6
Paramedics of male exam rooms	33.3	66.7	–	100.0	33.3	66.7

Table 4

Share of respondents with correct understanding of the clinical picture and methods of diagnosing breast cancer, %

Health care workers	Knowledge of the clinical picture and methods of diagnosis of breast cancer			
	Early symptoms of breast cancer	Clinical picture of an established breast cancer	Methods of diagnosing breast cancer	Term of palpation of the mammary glands
GP	25.0	–	–	75.0 %
Surgeons	50.0	–	–	–
Obstetrician-gynecologists	85.5	42.6	14.4	71.3
Paramedics of female exam rooms	57.4	14.4	–	57.2

It is difficult to explain the unsatisfactory competence of the respondents in the clinical symptomatology of the established breast cancer against the background of relatively sufficient knowledge of the early symptoms of breast cancer. Only 42.6 % of obstetrician-gynecologists and 14.4 % of paramedics of female exam rooms are well versed in this question. There is no single GP or surgeon who is competent in these issues. Also, GPs, surgeons and paramedics of female exam rooms are incompetent in the methods of diagnosing breast cancer. It is disappointing that among obstetrician-gynecologists, the majority (85.6 %) are also unaware of the full range of obligatory diagnostic methods for detecting breast cancer.

Only 71.3 % of obstetrician-gynecologists, three out of four GPs and half of the paramedics of female exam rooms know the basic principle of breast palpation, specifically the period of palpation to detect possible pathology, while no surgeon has any understanding of it.

Urologists and paramedics of male exam rooms are involved in the diagnosis of PC in rural areas. Analysis of the degree of competence of these specialists in the clinical picture, methods and stages of diagnostics of PC showed the following result: only two out of three urologists and one out of three paramedics of male exam rooms correctly realize the clinical picture of PC (Table 5). However, all specialists have a correct understanding of the tumor marker for PC, but none of them knows about all obligatory methods of examination in case of suspected PC; only one third of urologists are informed about the stages of PC diagnosis.

Only obstetrician-gynecologists and paramedics of female exam rooms are involved in the diagnosis of UC in the surveyed municipal districts. Their competence in comparison with the knowledge of those specialists who are involved in the diagnosis of the other three MNs is on a higher level (Table 6). First of all, this is due to the fact that the majority of obstetrician-gynecologists and paramedics of female exam rooms (85.5 %)

Table 5

Share of respondents with correct understanding of the clinical picture and methods of diagnosing PC, %

Health care workers	Knowledge of the clinical picture and diagnostic methods of PC			
	Clinical picture of PC	What is a tumor marker for PC	Diagnostic methods for BC	Diagnostic stages of PC
Urologists	66.7	100.0	–	33.3
Paramedics of male exam rooms	33.3	100.0	–	–

Table 6

Share of respondents with correct understanding of the clinical picture and diagnostic methods of UC, %

Health care UC workers	Knowledge of clinical picture and diagnostic methods					
	Clinical picture of UC		High-incidence symptom of UC in the period of menopause		Diagnostic methods for UC	
	know	do not know	know	do not know	know	do not know
Obstetrician-gynecologists	85.5	14.5	85.5	14.5	71.5	28.5
Paramedics of female exam rooms	85.5	14.5	71.5	28.5	57.3	42.7

correctly represent the clinical picture of UC. Moreover, they are well aware of the symptomatology of UC among women in menopausal period (85.5 % and 71.5 % of specialists, respectively).

The situation is slightly worse with the knowledge of the list of obligatory diagnostic methods for suspected UC: 71.5 % of obstetrician-gynecologists and 57.3 % of paramedics of female exam rooms fully know the necessary diagnostic methods.

Respondents were asked to make suggestions in the open question of the questionnaire on how to improve the negative situation caused by the high rate of MNs prevention. The activity of respondents regarding this issue was low.

As can be observed from the data obtained, almost every second respondent (57.3 %) proposed very unrealistic measures, which do not take into account the real situation of logistics supply and low availability of physicians working with mammographs in rural medical hospitals of the Chelyabinsk region. There is no doubt that continuous prostate-specific antigen (PSA) testing and mammography from the age of 40 will improve the diagnosis of MNs, but first of all there is a need for all physicians to increase their knowledge of diagnosing the early stages of MNs.

The medical workers' suggestions for reducing the distance between the attached CDH and outpatient oncology centers do not take into account the mutual location of cities and rural municipal areas in the region. The Regional Ministry of Health has to proceed from the situation that the cities,

which are the location of the CAOP, are more than 100 kilometers away from many rural settlements.

Certainly, it should be agreed with the suggestions of specialists that fluorography is uninformative in the diagnosis of early stages of LC, but there is no alternative substitute for it. The suggestion of the need for staffing of district oncologists is surely correct and has the potential to improve the situation of neglect in surveyed three of the five areas. It is not unexpected that suggestions for fines for violations in diagnosis, routing and dispensary monitoring of cancer patients were made by only a few respondents. Firstly, all serious violations are not left without material penalties under the system of labor remuneration under the "effective contract". Secondly, the implementation of fines for minor offenses in conditions of low staffing of rural hospitals with doctors will only exacerbate the problem of medical personnel in rural areas.

Conclusions

Thus, the study of rural PHC competence in diagnosing MNs of the main localizations revealed that serious problems related to subjective factors on the part of medical personnel have formed in rural municipal healthcare:

1) low oncological awareness and unsatisfactory competence of all surveyed medical workers regarding the early symptoms of MNs of the leading localizations;

2) a special reason of serious neglected cases is the inclusion of symptoms of the established MNs among the few early symptoms, in other words, the doctor, not sure of the diagnosis and focuses on the appearance of an obvious, from his point of view, symptom of the tumor, and as a result, the patient is diagnosed with a neglected stage of cancer;

3) flawed understanding of the full list of necessary diagnostic methods for MNs of the leading localizations, as well as the absolutely inadmissible fact of ignorance of the timing of breast palpation in suspected breast cancer;

4) unsatisfactory knowledge of normative documentation about routing of patients with suspected MNs by the majority of interviewed specialists, combined with understaffing of district oncologists, reduces the chances of patients to detect cancer at early stages.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions The study was planned, implemented, analyzed and described personally by the author.

Received: 03/28/2023
Revised version received: 04/06/2023
Accepted: 04/10/2024

Please cite this article in English as: Novikova S.V. Level of competence of rural physicians in primary health care in the diagnosis of malignant neoplasms of main localizations. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 112-122. DOI: 10.17816/pmj412112-122

CLINICAL CASE

Scientific Article
UDC 616.62-003.7-053: 616-056.7
DOI: 10.17816/pmj412123-129

HEREDITARY UROLITHIASIS AT A YOUNG AGE ON THE EXAMPLE OF A CLINICAL CASE

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НАСЛЕДСТВЕННЫЙ ХАРАКТЕР МОЧЕКАМЕННОЙ БОЛЕЗНИ В МОЛОДОМ ВОЗРАСТЕ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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To study the clinical features and course of urolithiasis in a young female patient, to suggest the cause of the simultaneous sudden formation of kidney stones in the patient and her mother within a year.

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Main provisions: urolithiasis (KSD) is one of the most common diseases of the urinary tract. The relevance of effective treatment of this problem arises from the steady increase in the number of patients around the world, especially in Russia. According to many researchers, this trend is due to the increase in life expectancy, changes in lifestyle and nutrition, as well as changes in the composition of water and climate conditions. Approximately two thirds of patients, develop the disease at the age from 30 to 60. Characteristic features of urolithiasis are repeated recurrence and a high incidence of complex forms, which complicates the treatment of such patients significantly.

Diagnostic algorithm and treatment of urolithiasis are demonstrated in this article on the example of a medical history of a young patient with rapidly progressing urolithiasis.

A similar disease with the same symptoms of urolithiasis was revealed in the patient's parent a week later, which suggests a hereditary predisposition factor or manifestation of urolithiasis being dependent on the hard drinking water.

The simultaneous sudden formation of kidney stones within a year in a patient at a young age and her mother emphasizes the hereditary nature of the disease. Probably, the peculiarities of national cuisine or the individual preferences of patients played a significant role in the development of the pathology. The composition of drinking water is extremely important. The patient is from the Republic of Bashkortostan, where water hardness is 7.8–8.0, which does not meet the standard.

Keywords. Rapidly progressing urolithiasis, young age, hereditary predisposition, hard drinking water.

Мочекаменная болезнь – одно из наиболее распространенных заболеваний мочевыводящих путей.

Необходимость эффективного лечения этой болезни обусловлена неуклонным ростом числа больных в мире, особенно в России. По мнению многих исследователей, эта тенденция обусловлена увеличением продолжительности жизни, изменением образа жизни и питания, а также изменением состава воды и климатических условий. Примерно у 2/3 больных заболевание развивается в возрасте от 30 до 60 лет. Характерной особенностью мочекаменной болезни является неоднократное рецидивирование и высокая распространенность сложных форм, что существенно осложняет ведение таких больных.

На примере истории болезни пациентки молодого возраста с быстро прогрессирующей мочекаменной болезнью показан алгоритм диагностики этого заболевания и продемонстрировано лечение, изучены особенности клиники и течения мочекаменной болезни, проанализированы причины одновременного внезапного образования камней в почках в течение года у пациентки. Аналогичное заболевание было выявлено у родительницы пациентки с теми же симптомами мочекаменной болезни спустя неделю, что позволяет предположить фактор наследственной предрасположенности или же зависимость проявления мочекаменной болезни от жесткости питьевой воды.

Одновременное внезапное образование камней в почках в течение года у пациентки в молодом возрасте и ее матери подчеркивает наследственную природу заболевания. Вероятно, немалую роль в развитии патологии сыграли особенности национальной кухни или индивидуальные предпочтения пациенток. Исключительное значение имеет состав питьевой воды. Пациентка проживает в Республике Башкортостан, где показатели жесткости воды 7,8–8,0, что не соответствует нормативу.

Ключевые слова. Быстро прогрессирующая мочекаменная болезнь, молодой возраст, наследственная предрасположенность, жесткая питьевая вода.

INTRODUCTION

Urinary tract stones have been part of the human condition for thousands of years – they were found even in Egyptian mummies [1]. In modern society, kidney stone disease, also known as urolithiasis, has become a particularly relevant issue. The incidence of this condition is quite high – 5–10 % of the population. The working-age group is particularly at risk for the disease [2].

Despite significant progress in the diagnosis and treatment of urolithiasis

(KSD), this pathology still occupies a leading position among diseases of the urinary system according to statistics. Over the past ten years, the incidence of KSD has been steadily increasing among the adult population in all regions of the Russian Federation [3]. Factors contributing to nephrolithiasis development include hereditary predisposition, living in hot, dry climates, a sedentary lifestyle, as well as disorders of the urinary tract such as hydronephrosis, impaired renal circulation, nephroptosis, renal polycystosis, and other conditions leading to urodynamic problems. The presence of a urinary tract infection, side effects of drug therapy, excessive consumption of oxalogenic products, table salt, sugar, insufficient intake of liquid and consumption of hard drinking water can also become a trigger for this disease. In recent years, numerous data have been accumulated on the role of nutritional factors in the etiology of nephrolithiasis, such as diet and food quality. Thus, increased consumption of animal protein can lead to high excretion of calcium, oxalates and urates, and a decrease in the level of citrate in urine [4]. Environmental degradation also contributes to the rise in the incidence of urolithiasis.

The objective of the study was to investigate the features of the clinical manifestations and the course of KSD in a young patient, to suggest the cause of simultaneous sudden formation of kidney stones during the year in the patient and her mother.

MATERIALS AND METHODS

The following studies were conducted as part of a complex examination:

1. Laboratory studies:

– complete urinalysis;

– blood analysis (general blood test, biochemical examination, coagulation tests);

2. Instrumental studies:

– ultrasound examination of the kidneys, bladder, and parathyroid glands;

– spiral computed tomography of the kidneys and upper urinary tract with intravenous bolus contrast.

CLINICAL CASE

The patient's medical history from 2023 was studied, as well as her complaints, anamnesis and results of general examination, laboratory and instrumental studies.

Patient G., 21 years old, first child, born from the third pregnancy. Pregnancy was accompanied by toxicosis. The labour was urgent, lasted 9 hours and 50 minutes. During the delivery, the umbilical cord was wrapped around the girl's neck. The amniotic fluid was cloudy and in small quantities. The birth weight was 3,600 grams, height – 52 cm, head circumference – 34 cm, chest circumference – 33 cm. The Apgar score was 5–7. The maximum weight loss was 220 g. The weight on discharge was 3,400 g.

On September 20th, 2023, she was admitted to the urology department of the First Republican Clinical Hospital in Izhevsk with complaints of severe aching pain in the left iliac region.

Development and course of the disease. The patient considers herself ill since June 2023, when a single microlith of the left kidney was detected during an ultrasound examination. The patient did not complain until September of the same year. On September 8th, 2023, intense pain suddenly appeared in the left iliac region, radiating along the ureter. The patient associates the occurrence of pain with the possible movement of the stone of the left kidney. On September 10th, 2023, she consulted a urologist at one of the paid clinics in Izhevsk. She was diagnosed with urolithiasis with a stone in the lower third of the left ureter. The patient was treated on an outpatient basis.

On the night of September 20th, 2023, her condition deteriorated sharply. She experienced intense aching pain in the left iliac region, up to loss of consciousness, nausea and vomiting, as well as vesical tenesmus. She did not call an ambulance. On the morning of September 20th, she went to the First Republican Hospital of Izhevsk on her own.

Upon objective examination, the condition was satisfactory. The skin and visible mucous membranes were physiologically colored. Peripheral lymph nodes were not enlarged, nor was the thyroid gland. There was no swelling. The lumbar region was symmetrical without deformation. Skin in the lumbar area was physiologically colored, temperature was normal, hydration was moderate, elasticity and turgor were normal. No swelling or redness was present. Palpation of kidneys (standing, lying in a supine position, right and left sides) showed that they are not palpable, but there is a positive concussion sign on the left side.

Laboratory studies. Complete urinalysis dated September 20th, 2023: color – brown, transparency – cloudy, density – 1,020 g/l, protein – 3 g/l, urobilinogen – 3.2 mmol/l, epithelial cells – 0–1 in the field of view, leukocytes – 0–1 in the field of view, fresh red blood cells in large quantities, bacteria in small quantities, mucus in a small amount.

In the general blood test dated September 20th, 2023, leukocytosis ($11.25 \cdot 10^9$/l) is noticeable.

Biochemical blood test dated September 21st, 2023: uric acid – 330.9 mmol/l, urea – 6.7 mmol/L, creatinine – 78 mmol/L, potassium – 3.90 mmol/L, sodium – 144.00 mmol/L, chlorine – 106.00 mmol/L.

Coagulogram dated September 21st, 2023: Quick-type PT – 94,000 %, prothrombotic time – 14,100 s, INR – 1,110, fibrinogen – 3,270 g/l, APTT – 29,200 s.

Instrumental studies. Ultrasound examination of the kidneys and bladder dated September 20th, 2023 (Figs. 1 and 2):

– Right kidney: size 10.2 × 4.2 cm, location is normal, contours are smooth, pelvicalyceal system (PCS) is not expanded, ratio of PCS to parenchyma is normal. Additional signs: a microlith in the upper calyx – 4 × 3 mm; a microlith in the lower calyx – 3.5 × 3 mm with shadowing. Area of adrenal glands without specific features.

– Left kidney: size 10.5 × 4.6 cm, normal location, smooth contours, PCS expanded and deformed (pelvis – 1.6 cm, calyx – 0.8 cm), ratio of PCS to parenchyma is normal. Additional signs: a microlith in the upper calyx, triangular shape, 4.2 × 2.0 mm with shadowing; a microlith in the lower calyx – 2.5 × 3 mm with shadowing. The lower third of ureter on the left expanded to 0.4 cm with the presence of internal structures in the form of a hyperechoic formation sized 7.0 × 4 mm with shadowing at 2.2 cm from the ureteral orifice. Discharge from the orifice on the left is slowed and weakened.

Conclusion: Ultrasound-signs of concretion in the lower third of the ureter on the left, concretions of both kidneys, urostasis on the left.

It should be noted that several microliths had already been detected in the patient compared to the data of June, 2023. This indicated a rapid progression of urolithiasis.

CT scan of the kidneys and upper urinary tract with intravenous bolus contrast dated September 22nd, 2023, reveals: concretion of the pelvicalyceal system of the right kidney; microliths of the pelvicalyceal system of both kidneys; partially streamlined concretion of the lower third of the left ureter; additional upper polar renal arteries on both sides; a simple cyst of the right kidney; scarring of the parenchyma of the left kidney.

Ultrasound examination of the thyroid and parathyroid glands on September 27th, 2023 did not reveal ultrasound signs of echopathology.

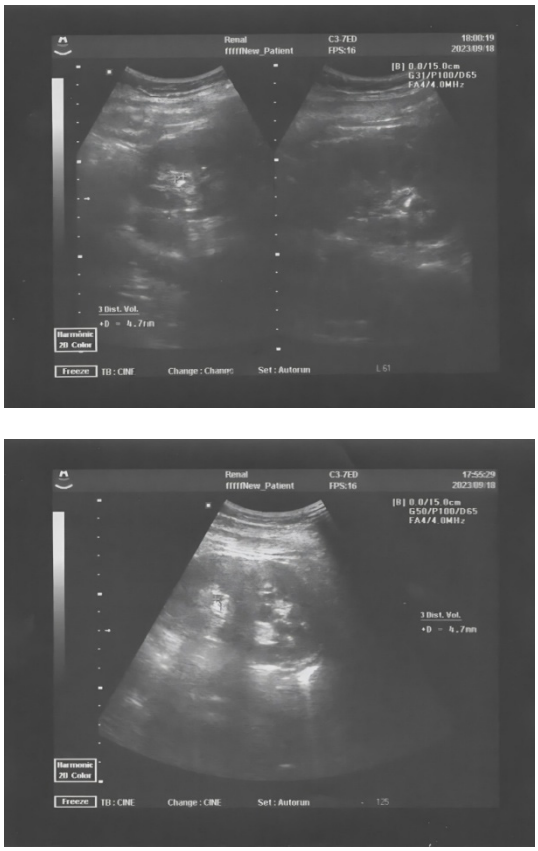

Fig. 1. Patient G. Ultrasound of the kidneys from September 20th, 2023. The presented images show microliths in the upper and lower calyces of the right and left kidney

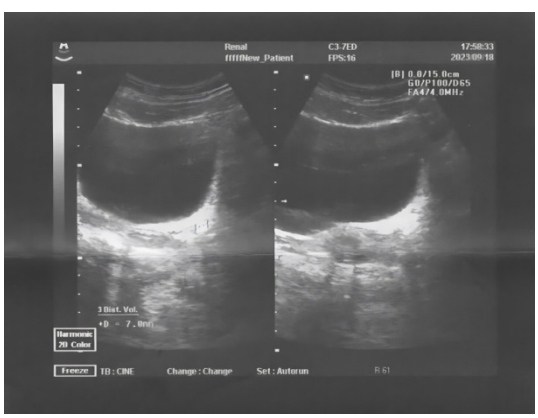

Fig. 2. Patient G. Ultrasound of the bladder from September 20th, 2023. Hyperechoic formation in the lower third of the ureter on the left

The following medication was administered in the hospital (22nd–26th of September, 2023): tamsulosin – 0.4; drotaverine – 2.0 (IV); 0.9 % NaCl – 500 ml (IV); ketorol – 2.0 (IM).

Surgical treatment: September 22nd, 25th and 27th, 2023 – remote lithotripsy of a stone of the lower third of the left ureter.

During the patient's stay in the hospital, transurethral contact lithotripsy was planned, but due to an improvement in the patient's condition (ultrasound revealed a 3.5 mm stone fragment in the lower third of the ureter, 1 cm from the ureteral orifice; the urostasis had been reduced), the operation was cancelled. The patient was discharged from the hospital with recommendations to follow.

A similar disease was detected in the patient's mother, who was admitted to the First Republican Clinical Hospital of Izhevsk with symptoms of renal colic a week after her daughter's admission to the hospital. She had not complained before. An ultrasound examination of the kidneys, adrenal glands and bladder was performed. Conclusion: ultrasound signs of calyceal pyelectasis of kidneys on the right with a microlith in the lower third of the ureter, concretion of the right kidney, perinephric effusion on the right.

Results and discussion

A possible cause of the formation of kidney stones in the patient is a hereditary predisposition factor, since the patient's mother had concretions in her right kidney and ureter a week after her daughter's hospitalization. Metabolic disorders, changes in the water-salt and chemical composition of the blood in patient G. were not detected. An anomaly was found: additional upper polar renal arteries on both sides, however the effect of renal abnormality on the development of KSD is unlikely. The quality and chemical composition of drinking water are of great importance. The patient lives in the Republic of Bashkortostan, where the water hardness is 7.8–8.0, which does not meet the normative indicators[1].

Diet therapy is very important in the treatment of recurrent urolithiasis. To achieve positive results, the patient was recommended to optimize her fluid intake, exclude products containing substances that contribute to the formation of stones, and diversify her diet. Such significant dietary changes should play a positive role in the treatment of this disease in the patient and allow to regulate the functioning of the urinary system in order to avoid relapses [5].

Conclusion

Thus, the development of urolithiasis is influenced by many factors. The urologist prescribes treatment and chooses gentle methods of treatment based on the individual characteristics of the patient. In this particular situation, the treatment was carried out in accordance with the clinical case of a particular patient and her medical history.

[1] Water hardness in the regions. Reference data, available at: https://aquaformula.ru/жесткость-воды-в-регионах-справочные/

Remote lithotripsy and symptomatic treatment (antispasmodic and anti-inflammatory therapy) were performed. The method of remote lithotripsy is widely used by urologists, as it is effective, and practically always gives positive results [6]. The patient was recommended litholytic therapy based on a shift in the pH of urine in the opposite direction to that in which a specific type of concretions is formed. A possible reason for the simultaneous sudden formation of kidney stones during the year in the patient and her mother is a hereditary predisposition and characteristics of water hardness in their place of residence, as well as the peculiarities of national cuisine.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 11/14/2023
Revised version received: 12/08/2023
Accepted: 03/15/2024

Please cite this article in English as: Styazhkina S.N., Sannikov P.G., Kuklin D.N., Gushchin S.G., Galieva R.Z., Khaydarova G.R. Hereditary urolithiasis at a young age on the example of a clinical case. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 123-129. DOI: 10.17816/pmj412123-129

Scientific Article
UDC 616-006.66
DOI: 10.17816/pmj412130-135

MIGRATION OF HEM-O-LOK CLIPS INTO THE BLADDER AFTER RADICAL PROSTATECTOMY – OWN EXPERIENCE

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МИГРАЦИЯ КЛИПС HEM-O-LOK В МОЧЕВОЙ ПУЗЫРЬ ПОСЛЕ РАДИКАЛЬНОЙ ПРОСТАТЭКТОМИИ – СОБСТВЕННЫЙ ОПЫТ

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Non-absorbable polymer Hem-o-Lok clips are widely used during nerve-sparing radical prostatectomy for clipping of the neurovascular bundle, as well as for rapid knotless fixation of sutures during the formation of urethrovesical anastomosis. At the same time, cases of migration of Hem-o-Lok clips into the bladder at various times after RP have been described.

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Our retrospective analysis of 1321 patients, who underwent laparoscopic radical prostatectomy at A.M. Granov Russian Scientific Center of Radiology and Surgical Technologies from 2014 to 2023, revealed 3 cases of Hem-o-Lok clip intravesical migration. Also, to search for similar cases of this rare complication a literature review was conducted.
The frequency of postoperative intra-bladder clip migration in our study was 0.23 % (3/1321). One case of spontaneous clip passage was observed 3 months later the radical prostatectomy. In two other cases, long-term symptoms of dysuria (in 7 months and 4 years, respectively) revealed clip incrustation, which led to the removal of the clips through endoscopic intervention and laser cystolithotripsy.
Despite the low incidence of this complication, the use of Hem-o-Lok clips during laparoscopic radical prostatectomy, should be minimized reasonably, particularly during the urethro-vesical anastomosis formation. If lower urinary tract symptoms and/or hematuria occur at any point in the postoperative period, it's advisable to conduct an instrumental examination of the bladder to rule out potential clip migration and possible incrustation.
Keywords. Laparoscopic radical prostatectomy; Hem-o-lok clip migration.

Нерассасывающиеся полимерные клипсы Hem-o-Lok широко применяются в ходе выполнения нервосберегающей радикальной простатэктомии для клипирования сосудисто-нервного пучка, а также для быстрой безузловой фиксации нитей при формировании уретровезикального анастомоза. Вместе с тем описаны случаи миграции клипс Hem-o-Lok в полость мочевого пузыря в различные сроки после радикальной простатэктомии.
Ретроспективный анализ послеоперационного наблюдения 1321 пациента, перенесшего эндовидеохирургическую радикальную простатэктомию в отделении оперативной онкоурологии РНЦРХТ им. акад. А.М. Гранова с 2014 по 2023 г., выявил 3 случая внутрипузырной миграции клипс Hem-o-Lok. Также проведен литературный поиск случаев развития данного редкого осложнения.
Частота встречаемости послеоперационной миграции клипс в мочевой пузырь в нашем исследовании составила 0,23 % (3/1321). В одном случае имело место самостоятельное отхождение клипсы через 3 месяца после радикальной простатэктомии. В двух других осложнение манифестировало в отдаленные сроки (через 7 месяцев и 4 года соответственно) клиникой дизурии на фоне инкрустации клипс, что потребовало эндоскопического вмешательства с лазерной цистолитотрипсией и их удаления.
Несмотря на низкий процент развития данного осложнения, необходимо разумно минимизировать использование клипс Hem-o-Lok в ходе радикальной простатэктомии, особенно при формировании уретровезикального анастомоза. При появлении соответствующих симптомов нижних мочевых путей и/или макрогематурии в любые отдаленные сроки послеоперационного периода целесообразно выполнить инструментальное обследование мочевого пузыря с целью исключения миграции клипсы и ее возможной инкрустации.
Ключевые слова. Эндовидеохирургическая радикальная простатэктомия; миграция клипсы Hem-o-lok.

INTRODUCTION

The first introduced in 1999, Hem-o-Lok clips (Weck Surgical Instruments, Teleflex Medical, Durham, NC, USA) are widely used in various minimally invasive endovideosurgical procedures now [1–6]. In the process of radical prostatectomy (RPE), these non-absorbable polymer clips are used during lateral dissection to clip the neurovascular bundle (NVB) as well as for rapid knotless thread fixation during con (UVA). Furthermore, the migration of Hem-o-Lok clips into the bladder cavity at various times after RPE has been described. This complication occurs in 1–1.5 % of cases and usually progresses during the first year after surgery [1; 7–9].

The aim of the study is to demonstrate our own results of diagnosis and treatment of cases of Hem-o-Lok clips migration into the bladder cavity after radical prostatectomy.

MATERIALS AND METHODS

1321 endovideosurgical RPEs were conducted at the Department of Operative Oncourology of the „Russian Scientific Center of Radiology and Surgical Technologies named after A.M. Granov“ from 2014 to 2023. During the intervention, Hem-o-Lok clips were used for clipping the vascular pedicles of the prostate gland, for dissection in the SNP area, as well as for fixation of two threads for 12 parts of the conditional dial after UVA formation according to the technique of Van Velthoven et al. [9]. Postoperative follow-up was performed routinely every three months for the first year, then every six months for five years and annually. During the follow-up period, three cases of Hem-o-Lok clips migrating into the bladder cavity were identified [1].

RESULTS

The frequency of this complication in our study is 0.23 % (3 out of 1321). Three months after surgery, the first patient had an independent detachment of the Hem-o-Lok clip during urination without complaints of dysuria or hematuria. The patient underwent endovideosurgical RPE without NVB preservation for localized PC. The Hem-o-Lok clip was used to fixate two V-loc threads on the 12 parts of the conditional dial after UVA formation (Fig. 1). In this case, there was probably a displacement of the clip into the area of the UVA margins with its subsequent prolapse into the bladder cavity. After resorption of the threads, the clip migrated into the bladder cavity and detached on its own during the next urination. Currently, the patient is under dynamic follow-up, fully holds urine, has no complaints of dysuria.

For the second patient, Hem-o-Lok clips were used for lateral dissection during laparoscopic RPE with preservation of the right NVB. In retrospective analysis of the surgery recording, it was found that one of the clips was inappropriately applied and fixed to the NVB tissue only in the area of its lock (Fig. 2). The patient complained to the urologist at the clinic of the place of residence about discomfort and pain during urination and thinning of the urine stream after seven months of surgery. The patient received

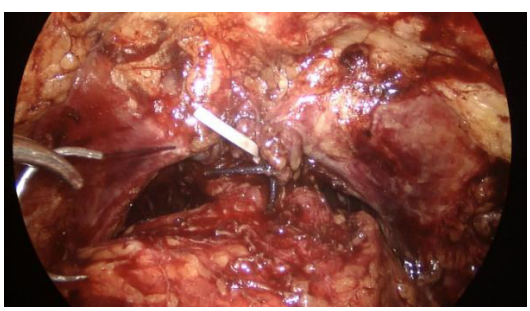

Fig. 1. Hem-o-Lok clip fixing the UVA threads

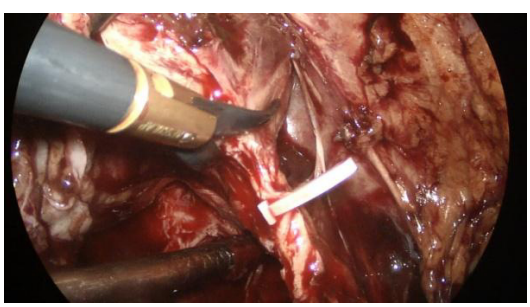

Fig. 2. Inappropriately applied clip Hem-o-Lok clip on the right NVB

[1] All patients' rights were reserved. The study was conducted within the framework of bioethics rules and was retrospective.

conservative anti-inflammatory and antibacterial therapy without positive effect. A single bouginage had no effect. During examination, ultrasound and MRI of the bladder revealed a non-displaced concretion, which was 3 cm in diameter, fixed to the posterior wall of the urinary bladder cervix (Fig. 3). The patient underwent laser cystolithotripsy, urethrocystoscopy. After fragmentation of the stone, a Hem-o-Lok clip was detected with one end immersed in the bladder wall. The clip was clamped and removed using forceps. The postoperative period proceeded without any complications. Complaints of dysuria are completely resolved; the patient can hold urine.

The third patient underwent endovideosurgical RPE with preservation of both NVBs also using Hem-o-Lok clips. The postoperative period was uneventful; the patient holds urine from the first day of catheter removal. There was a gradual deterioration of urination, thinning of the urine stream and occasional impurity of blood in the urine after 4 years and 2 months after surgery. The patient was taking alpha-adrenoblockers and phytopreparations with no significant positive effect. During examination, CT scan of the pelvis revealed an irregularly shaped bladder concrement fixed to its posterior wall with the dimensions of 3 4 cm (Fig. 4). The patient underwent urethrocystoscopy with laser cystolithotripsy. Six Hem-o-Lok clips were detected after stone fragmentation, immersed in the thickness of the posterior wall of the urinary bladder cervix at different depths (Fig. 5). There was performed photovaporization of scar tissues around the clips with their subsequent removal with forceps. The postoperative period proceeded without complications, the urethral catheter was removed on the fourth day. The complaints of dysuria and hematuria are resolved; the patient holds urine completely.

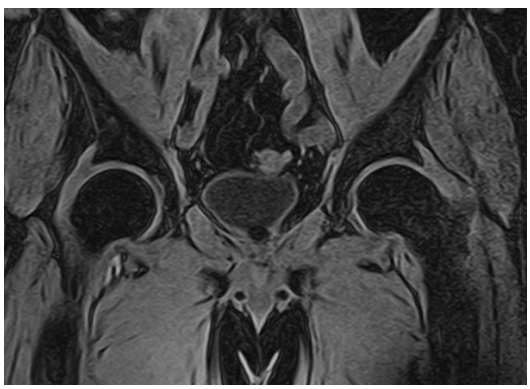

Fig. 3. MR image of a non-displaced concrement, which was 3 cm in diameter, fixed to the posterior wall of the urinary bladder cervix

Fig. 4. CT scan of a concrement bladder

Fig. 5. Removed Hem-o-Lok clips and fragmented concrement

RESULTS AND DISCUSSION

According to the clinical manifestations accompanying the position of the clip in the bladder cavity, Yu et al. distinguish three types of Hem-o-Lok clip migration. The first type occurs when the clip erodes the immediate area of the UVA with the development of obstructive dysuric symptoms to the formation of urinary bladder cervix contracture and urethral stricture. The second type occurs when the clip penetrates into the bladder lumen at a short distance from the UVA and it is accompanied by encrustation and recurrent macrohematuria. At last, the independent detachment of the clip during urination a few weeks after RPE is considered, as the third type of clip migration [8].

The mechanism of clip migration into the bladder cavity and erosion of the bladder wall is not completely clear. The frequency of this complication does not exceed 1–1.5 % of all cases and usually occurs in the first year after surgery [1]. However, single cases of this complication have been described in the literature after 10 and 11 years after RPE [4; 5]. It is often that multiple clips migrate at the same time or it is rarely, that one clip at a time, sequentially over several years [2]. The first and second types of clips are removed endoscopically under vision control with forceps or with laser or transurethral resection [3; 7].

In accordance with the classification of Yu et al. three cases of intravesical migration of clips were identified in our study: there were two patients with the second type and one patient with the third type. The case of independent clip detachment after RPE occurred at an early time with no complaints of dysuria. In two other cases, the complication occurred in remote terms (in 7 months and 4 years, accordingly) with the clinic of dysuria due to the incrustation of clips, which required endoscopic intervention with laser cystolithotripsy and their removal.

CONCLUSIONS

The use of Hem-o-Lok clips during laparoscopic prostatectomy is connected with the risk of their migration into the bladder lumen. Our experience demonstrates that this complication can occur in different terms of the postoperative period and in the case of fixed clips is accompanied by dysuric symptoms or macrohematuria. It is necessary to carefully observe the surgical technique, minimize the use of Hem-o-Lok clips, especially during UVA formation, and timely intraoperatively remove fallen and improperly applied clips, to prevent clip migration. In case a patient complains of lower urinary tract symptoms and/or macrohematuria at any time after endovideosurgical RPE, radiologic examination of the bladder should be performed to exclude migration of the clip and its possible encrustation.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions are equivalent.

Received: 01/09/2024
Revised version received: 03/14/2024
Accepted: 03/15/2024

Please cite this article in English as: Bogomolov O.A., Sukhanova T.V., Shkolnik M.I., Kneev A.Yu., Dolbov A.L., Artemov M.V. Migration of Hem-O-Lok clips into the bladder after radical prostatectomy – own experience. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 130-135. DOI: 10.17816/pmj412130-135

CLINICAL STUDIES

Scientific Article
UDC 616.53-002.25
DOI: 10.17816/pmj412136-141

COMPARATIVE EVALUATION OF THE EFFECTIVENESS AND SAFETY OF ACNE TREATMENT WITH SYSTEMIC ISOTRETINOIN IN MONOTHERAPY AND TOGETHER WITH COMBINED ORAL CONTRACEPTIVES IN WOMEN

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СРАВНИТЕЛЬНАЯ ОЦЕНКА ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ ЛЕЧЕНИЯ АКНЕ У ЖЕНЩИН СИСТЕМНЫМ ИЗОТРЕТИНОИНОМ В МОНОТЕРАПИИ И СОВМЕСТНО С КОМБИНИРОВАННЫМИ ОРАЛЬНЫМИ КОНТРАЦЕПТИВАМИ

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Objective. To give a comparative evaluation of the effectiveness and safety of acne treatment with systemic isotretinoin in monotherapy and together with combined oral contraceptives in women.
Materials and methods. 65 women with severe papulo-pustular acne took part in the study. They were divided into two groups: group I consisted of 35 women who used systemic isotretinoin for acne in monotherapy; group II included 30 women who took systemic isotretinoin together with combined oral contraceptives. A comprehensive clinical and laboratory study was conducted. The study included a biochemical blood test to

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determine the lipid profile, liver transaminases, and hormonal homeostasis. The obtained results were analyzed using the methods of parametric and nonparametric statistics, the standard error (m) was used in the calculations, the level of statistical significance was noted at $p < 0.05$.
Results. In women treated for acne with systemic isotretinoin in monotherapy relief occurs in 4 weeks, and complete clinical recovery in 24 weeks after the beginning of therapy; when using systemic isotretinoin together with combined oral contraceptives, relief is determined in 2 weeks, and complete clinical recovery in 16 weeks of treatment. The main side effects of systemic isotretinoin were cheilitis, skin xerosis, retinoic dermatitis and telogen alopecia. Cheilitis was revealed in the majority of patients in both groups equally. Xerosis of the skin, retinoic dermatitis and telogen alopecia were more often observed in the 1st group. In women of the 1st group, the level of progesterone was significantly higher and the level of estradiol was lower than in women of the 2nd group.
Conclusions. Systemic isotretinoin has shown high efficacy and safety in treatment for acne in women. Combined oral contraceptives normalize hormonal homeostasis, which helps to eliminate acne. When using systemic isotretinoin in combination with combined oral contraceptives, the main clinical effect occurs earlier, and adverse reactions are less frequent and less severe than in monotherapy. The combined use of systemic isotretinoin and combined oral contraceptives is the optimal method of acne treatment in women.
Keywords. Systemic isotretinoin, combined oral contraceptives, main clinical effect, side effect.

Цель. Дать сравнительную оценку эффективности и безопасности лечения акне у женщин системным изотретиноином в монотерапии и в сочетании с комбинированными оральными контрацептивами.
Материалы и методы. В исследовании приняли участие 65 женщин с тяжелыми папулопустулезными акне, которые составили две группы: I группа – 35 женщин, использующих для лечения акне системный изотретиноин в монотерапии; II группа – 30 женщин, применяющих системный изотретиноин в сочетании с комбинированными оральными контрацептивами. Проведено комплексное клинико-лабораторное исследование, включающее биохимический анализ крови с определением показателей липидного спектра, печеночных трансаминаз, гормонального гомеостаза. Анализ полученных результатов выполнен с помощью методов параметрической и непараметрической статистики, при расчетах использовалась стандартная ошибка (m), уровень статистической значимости был отмечен при $p < 0{,}05$.
Результаты. У женщин с акне при применении системного изотретиноина в монотерпии улучшение наступает через 4 недели, а полное клиническое выздоровление – через 24 недели от начала терапии; при использовании системного изотретиноина в сочетании с комбинированными оральными контрацептивами улучшение возникает через 2 недели, а полное клиническое выздоровление – через 16 недель лечения. Основными побочными эффектами системного изотретиноина являлись хейлит, ксероз кожи, ретиноевый дерматит и телогеновая алопеция. Хейлит был отмечен у подавляющего большинства пациенток, одинаково в обеих группах. Ксероз кожи, ретиноевый дерматит и телогеновая алопеция чаще наблюдались у женщин, применяющих системные ретиноиды в монотерапии. У женщин с акне, использующих системный изотретиноин в монотерапии, достоверно выше уровень прогестерона и ниже значение эстрадиола, чем у женщин, применяющих системный изотретиноин совместно с комбинированными оральными контрацептивами.
Выводы. Системный изотретиноин показал высокую эффективность и безопасность при лечении акне у женщин. Комбинированные оральные контрацептивы нормализуют гормональный гомеостаз, что способствует устранению акне. При применении системного изотретиноина совместно с комбинированными оральными контрацептивами основной клинический эффект наступает раньше, а побочные реакции встречаются реже и менее выражены, чем при монотерапии системным изотретиноином. Сочетанное использование системного изотреиноина и комбинированных оральных контрацептивов является оптимальным методом лечения акне у женщин.
Ключевые слова. Системный изотретиноин, комбинированные оральные контрацептивы, основной клинический эффект, побочное действие.

INTRODUCTION

The name of dermatosis "acne" has ceased to be used with the definition of "youthful" for a long time, because this disease can proceed or even occur after pubertal age. Moreover, it is mainly observed among women [1; 2]. E.R. Araviyskaya marks that about 20 % of adult women are concerned about the appearance of acne on the chin before menstruation [3]. Systemic isotretinoin, hormonal therapy, antibacterial agents, and azelaic acid are used externally to treat acne among women [4]. Antibacterial therapy suppresses the activity of *C. acnes* and has a remarkable anti-inflammatory effect [5]. Azelaic acid has primarily anticomedogenic and keratolytic effects [6]. Combined oral contraceptives are predominantly used among hormonal preparations [7]. These combined oral contraceptives reduce absolute and relative hyperandrogenemia, contributing to the reduction of sebum production, which is a key factor in the progression of acne [8]. Systemic isotretinoin affects all components of acne pathogenesis: it inhibits the function of sebaceous glands, eliminates follicular hyperkeratosis and has antibacterial and anti-inflammatory effects [9]. It is important to remember that systemic isotretinoin is teratogenic, therefore, women should avoid pregnancy during treatment and for one month after its termination [10]. Many people use combined oral contraceptives for this purpose, the effect of which was mentioned above [11].

The aim of the study is to provide a comparative evaluation of the efficiency and safety of acne treatment among women with systemic isotretinoin in monotherapy and in combination with combined oral contraceptives.

MATERIALS AND METHODS

The retrospective study was conducted on the basis of the inpatient department of the regional skin and venereological dispensary of the Perm region and medical centers A2Med and „Genesis“. Sixty-five women with serious papulopustular acne in the age range of 20–35 years participated in the study. There were distinguished two groups. The first group consisted of 35 women using systemic isotretinoin of 0.5 mg/kg per day in monotherapy for acne treatment; the second group consisted of 30 women using systemic isotretinoin of 0.5 mg/kg per day in combination with combined oral contraceptives. The groups were comparable in social and somatic status, body weight and height, all were residents of the Perm region, and all gave voluntary informed consent to participate in the study. The exclusion criteria were serious endocrine pathology, gynecological diseases in anamnesis, cardiovascular diseases, liver and kidney pathology, smoking, alcoholism, use of external medications for acne treatment.

A comprehensive clinical and laboratory examination was conducted. There were studied the complaints and made anamnesis of the disease and life, assessed the general condition of the body, examination of skin and mucous membranes, general blood and urine tests, biochemical blood analysis with determination of lipid spec-

trum, hepatic transaminases, hormonal homeostasis. The results were analyzed using the methods of parametric and nonparametric statistics using Microsoft Excel and Statistica 5.1 for Windows (Stat Inc., USA). The standard error (m) was used in the calculations, and the level of statistical significance was noted at $p < 0.05$.

Results and discussion

Most women with serious papulopustular acne, who receive systemic isotretinoin in monotherapy, have improvement after 4 weeks and complete clinical recovery after 24 weeks from the beginning of therapy. Most improvement occurs after 2 weeks and complete clinical recovery occurs after 16 weeks of treatment among women with serious papulopustular acne, who receive systemic isotretinoin in combination with combined oral contraceptives (Table 1).

The most common side effects of systemic isotretinoin in the course of treatment of serious papulopustular acne among women were cheilitis, xerosis, retinoid dermatitis, and telogen alopecia. Cheilitis was observed among the vast majority of patients equally in both groups. Xerosis, retinoid dermatitis, and telogen alopecia were more frequently observed among women receiving systemic isotretinoin in monotherapy (Table 2).

Women with serious papulopustular acne who receive systemic isotretinoin in monotherapy have significantly higher progesterone level and lower estradiol value than women using systemic isotretinoin in combination with combined oral contraceptives (Table 3).

Combined oral contraceptives eliminate hyperandrogenemia, and this results in decreased production and normalization of sebum chemistry. In this process, follicular hyperkeratosis and inflammatory response of the pilosebaceous follicle are indirectly reduced. Thus, combined oral contraceptives enhance the primary effect of systemic isotretinoin. In addition, estrogens, which are part of combined oral contraceptives, have a softening and moisturizing effect on the skin, giving it elasticity and softness, which can smooth unwanted adverse reactions of systemic isotretinoin.

Table 1

Specific features of the progression of the primary effect of systemic isotretinoin in combination with monotherapy and combined oral contraceptives (% ± *m*)

Primary clinical effect	Group I, $n = 35$	Group II, $n = 30$	p
Occurrence of improvement after 2 weeks	22.9 ± 7.1*	73.3 ± 8.1	0.004
Occurrence of improvement after one month	77.1 ± 7.1*	26.7 ± 8.1	0.004
Complete clinical recovery after 16 weeks	14.3 ± 5.9*	80.0 ± 7.3	0.001
Complete clinical recovery after 24 weeks	85.7 ± 5.9*	20.0 ± 7.3	0.001

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives, *$p < 0.05$.

Table 2

Specific features of side effects during monotherapy of systemic isotretinoin and in combination with oral contraceptives (% ± *m*)

Side effect	Group I, $n = 35$	Group II, $n = 30$	p
Cheilitis	91.4 ± 4.7	86.6 ± 6.2	0.537
Xerophthalmia and conjunctivitis	14.3 ± 5.9	10.0 ± 5.5	0.540
Nasal hemorrhage	11.4 ± 5.4	10.0 ± 5.5	0.853
Xerosis	60.0 ± 8.3*	26.7 ± 8.1	0.007
Retinoid dermatitis	45.7 ± 8.4*	16.7 ± 6.8	0.012
Telogen alopecia	42.8 ± 8.4*	13.3 ± 6.2	0.009
Paronychia and onychodystrophy	8.6 ± 4.7	6.7 ± 4.6	0.774
Headache, depression	5.7 ± 3.9	10.0 ± 5.5	0.518
Arthralgias and myalgias	5.7 ± 3.9	6.7 ± 4.6	0.873
Anemia	5.7 ± 3.9	6.7 ± 4.6	0.873
Hyperlipidemia	11.4 ± 5.4	10.0 ± 5.5	0.853
Increasing of liver transaminase level	8.6 ± 4.7	6.7 ± 4.6	0.774

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives, $^*p < 0.05$.

Table 3

Characteristics of hormonal homeostasis among women with acne during treatment using systemic isotretinoin in monotherapy and in combination with oral contraceptives (% ± *m*)

Indicators of hormonal homeostasis	Group I, $n = 35$	Group II, $n = 30$	p
Absolute hyperandrogenemia	17.1 ± 6.4	6.7 ± 4.5	0.366
Hyperprogesteronemia	62.9 ± 8.2*	10.0 ± 5.5	0.001
Decreasing estradiol level in the blood	34.3 ± 8.0*	6.7 ± 4.5	0.006

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives, $^*p < 0.05$.

CONCLUSIONS

1. Systemic isotretinoin has shown high efficiency and safety in the process of treatment from acne among women.

2. Combined oral contraceptives normalize hormonal homeostasis, which helps to eliminate acne.

3. When systemic isotretinoin is used in combination with combined oral contraceptives, the primary clinical effect occurs earlier, and side effects are less frequent and less serious than with the use of systemic isotretinoin monotherapy.

4. The combined use of systemic isotretinoin and combined oral contraceptives

is the optimal treatment for acne among women.

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Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions:

Elkin V.D. – was involved in data analysis, gave final approval of the manuscript sent to the editorial office.

Kobernik M.Y. – contributed to the concept and design of the study, acquisition, analysis and interpretation of data; prepared the first version of the article.

Received: 01/23/2024
Revised version received: 03/06/2024
Accepted: 03/15/2024

Please cite this article in English as: Elkin V.D., Kobernik M.Yu. Comparative evaluation of the effectiveness and safety of acne treatment with systemic isotretinoin in monotherapy and together with combined oral contraceptives in women. *Perm Medical Journal*, 2024, vol. 41, no. 2, pp. 136-141. DOI: 10.17816/pmj412136-141

Scientific and practical publication

PERM MEDICAL JOURNAL

2024. Vol. XLI. No. 2

Editor and corrector M.N. Afanaseva

The date of publication is 25.04.2024. Format 84×108/16.
Edition is 50 copies. The price is free.

Printed by Individual Enterpreneur Seregina O.N.
Adress: ap. 174, 21 Metallistov st., Perm, 614107, Russia.