Scientific medical journal

Medical Herald of the South of Russia

Founder – Rostov State Medical University
Publication Frequency: Quarterly

Vol. 12 № 1 2021
(January–March)

Научный медицинский журнал

Медицинский вестник Юга России

Учредитель – ФГБОУ ВО РостГМУ Минздрава России
Издание выходит ежеквартально

Т. 12 № 1 2021
(январь–март)

Адрес редакции и издателя:
344022, Ростов-на-Дону, пер. Нахичеванский, 29
E-mail: rostgmu-journal@rambler.ru
Тел. +79286116608

Postal address:
29, Nakhichevansky Lane, Rostov-on-Don 344022 Russia
E-mail: rostgmu-journal@rambler.ru
Tel. + 79286116608

Цена свободная.
Подписной индекс 43783 в каталоге «Пресса России».

Дизайн, верстка – типография
ФГБОУ ВО РостГМУ Минздрава России, 2021 г.
344022, Ростов-на-Дону, пер. Нахичеванский, 29

Дата выхода в свет Зак.
Тираж 1000.

Зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор) ПИ № ФС 77 - 76526 от 2 августа 2019 г.

Журнал рекомендован ВАК Министерства образования и науки РФ для опубликования основных результатов на соискание учёной степени доктора и кандидата медицинских наук по специальностям: 14.01.01 – Акушерство и гинекология, 14.01.02 – Эндокринология, 14.01.04 – Внутренние болезни, 14.01.05 – Кардиология, 14.01.06 – Психиатрия, 14.01.08 – Педиатрия; 14.01.09 – Инфекционные болезни; 14.02.02 – Эпидемиология; 14.02.04 – Медицина труда; 14.03.09 – Клиническая иммунология, аллергология. Все статьи публикуются бесплатно.

Материалы представленных статей рецензируются согласно требованиям к публикациям, регламентированным ВАК.

СОДЕРЖАНИЕ:

Обзоры

Оригинальные статьи

Клинические случаи

Обмен опытом

Юбилей

CONTENTS:

Reviews

Original articles

Clinical cases

Exchange of experience

Anniversary

УДК: 616.71-007.234-008.9+575.191
DOI 10.21886/2219-8075-2021-12-1-6-13

The role of genetic and metabolic disorders in osteoporosis

L.V. Vasilyeva, E.N. Bezzubtseva, E.V. Gosteva, E.F. Evstratova

N. N. Burdenko Voronezh State Medical University, Voronezh, Russia

Osteoporosis is a progressive multifactorial systemic disease of the skeletal system characterized by the damage of the microarchitectonics of the bone tissue, which leads to the occurrence of low-energy fractures and impairment of the quality of life of individuals. The risk factors for the development of osteoporosis include smoking, which inhibits calcium absorption in the intestine and not only contributes to the reduction of bone density but also acts as a predictor of bronchopulmonary pathology. The systemic inflammation that develops in patients with chronic obstructive pulmonary disease, associated with the production of interleukins (IL)-6, IL-1, IL-8, and tumor necrosis factor – α, stimulates osteoclast-mediated bone resorption and a low level of osteoprotegerin closes the circle. In clinical practice, the determination of markers of bone resorption is required. This is a tartrate-resistant acid phosphatase, the 5β fraction of which signals the end of the resorption process; these are hydroxypyridine crosslinks – pyridoline (PYD) and deoxypyridoline, that stabilize the bone collagen molecule. Genetic factors also play an important role in the development of osteoporosis. The presence of the GG genotype or the G allele of the 283 A> G polymorphism (Bsml) of the VDR gene is a predictor of osteoporosis of the lumbar vertebrae L1-L4. The substitution of cytosine for thymine (C> T) in exon 17 of the calcitonin gene (CALCR) at position 1340 leads to the substitution of the amino acid proline (CCG) for leucine (CTG) at position 463 of the receptor protein molecule and affects bone density. But the most phylogenetically ancient mechanism for regulating the development and maintenance of tissue homeostasis by controlling cell proliferation, differentiation, migration, and apoptosis is the Wnt signaling pathway (SP-Wnt). Alterations in Wnt signaling observed in cases of genetic mutations cause various diseases of the human skeleton. A systematic literature search was carried out using the Scopus, PubMed, Web of Science databases.

Keywords: osteoporosis, osteoprotegerin, gene polymorphism, review.

For citation: Vasilyeva L.V., Bezzubtseva E.N., Gosteva E.V., Evstratova E.F. The role of genetic and metabolic disorders in osteoporosis. *Medical Herald of the South of Russia.* 2021;12(1):6-13. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-6-13.

Corresponding author: Ekaterina N. Bezzubtseva bezzubtsewa.ekaterina@yandex.ru.

Роль генетических и метаболических нарушений при остеопорозе

Л.В. Васильева, Е.Н. Беззубцева, Е.В. Гостева, Е.Ф. Евстратова

Воронежский государственный медицинский университет им. Н.Н. Бурденко, Воронеж, Россия

Остеопороз — это прогредиентное мультифакториальное системное заболевание скелета, характеризующееся нарушением микроархитектоники костной ткани, приводящее к возникновению низкоэнергетических переломов и ухудшающее качество жизни индивидуумов. К факторам риска развития остеопороза относят курение, которое за счёт ингибирования всасывания кальция в кишечнике не только способствует развитию снижению плотности костной ткани, но и является предиктором возникновения бронхолёгочной патологии. Развивающееся при хронической обструктивной болезни легких системное воспаление, связанное с выработкой интерлейкинов (ИЛ)-6, ИЛ-1, ИЛ-8, фактора некроза опухоли α, стимулирует остеокластопосредованную резорбцию костной ткани, а низкий уровень остеопротогерина замыкает порочный круг. В клинической практике требуется определение маркеров резорбции костной ткани. Это и тартрат-резистентная кислая фосфатаза, 5β фракция которой сигнализирует об окончании процесса резорбции; это и гидроксипиридиновые сшивки (пиридолин (PYD) и деоксипиридолин), придающие стабилизацию молекуле костного коллагена. В развитии остеопороза не последнюю роль играют и генетические факторы. Наличие генотипа GG или аллеля G полиморфизма 283 A> G (Bsml) гена VDR является предиктором остеопороза поясничных позвонков L1-L4. Замена цитозина на тимин (C> T) в экзоне 17 гена кальцитонина (CALCR) в положении 1340 ведёт к замене аминокислоты пролина (CCG) на лейцин (CTG) в положении 463 молекулы белка-рецептора и влияет на плотность кости. Но наиболее филогенетически древним механизмом регуляции развития и поддержания гомеостаза тканей за счёт контроля пролиферации, дифференциации, миграции и апоптоза клеток является сигнальный путь Wnt (СП-Wnt). Изменения в передаче сигнала Wnt, наблюдаемые при генетических мутациях, вызывают различные заболевания скелета человека. Системный поиск литературы проводился по базам данных Scopus, PubMed, Web of Science.

Ключевые слова: остеопороз, остеопротогерин, полиморфизм генов, обзор.

Для цитирования: Васильева Л.В., Беззубцева Е.Н., Гостева Е.В., Евстратова Е.Ф. Роль генетических и метаболических нарушений при остеопорозе. *Медицинский вестник Юга России.* 2021;12(1):6-13. DOI 10.21886/2219-8075-2021-12-1-6-13.

Контактное лицо: Беззубцева Екатерина Николаевна, bezzubtsewa.ekaterina@yandex.ru.

Osteoporosis is a progressive multifactorial systemic disease of the skeletal system that is manifested by a decrease in the bone mass and characterized by the damage of the microarchitecture of the bone tissue, which leads to the brittleness of the bones [1].

According to the World Health Organization, around 75 million people around the world suffer from osteoporosis. The main risk group (around 80%) is represented by menopause women, i.e. the disease is associated with age-related changes in metabolic processes. Thus, the risk of its development should be defined after 45 years old. In industrially developed countries, senile osteoporosis is widespread in men and women after 70 years old. Drug-induced secondary osteoporosis or associated with different pathology is also widespread. It is expected that annually the rate of femoral neck fractures will increase from 1.7 mln (1990) to 6.3 mln by 2050 [2].

The risk factors for the development of osteoporosis can be divided into genetically-related (non-modifiable) and modifiable. The role of genetic predisposition is doubtless, as well as the influence of such external factors as vitamin D deficit, lack of protein in food, hypodynamia, low body weight, glucocorticoid therapy, external breathing disturbances, smoking [3].

Smoking increases the risk of osteopathic fractures of different localization by 1.29 times, femoral neck fractures – by 1.8 times [4] because of disturbances in osteogenesis that result from a decrease in the intestinal absorption of calcium [5]. The density of bone tissue in smokers (more than 20 packs/years) is 16% lower in comparison with non-smokers [6]. The risk of vertebra and femoral bone fracture in smokers is higher than in non-smokers. In ex-smokers, the parameters of the mineral density of bone tissue T were 0.064 units higher per every 10 years of remission [7]. Smoking not only contributes to a decrease in the density of bone tissue but is also a predictor of the development of bronchopulmonary pathology, which in turn, induces pulmonogenic osteopenias.

The rate of occurrence of osteopenia in patients with chronic obstructive pulmonary disease (COPD) varies from 60 to 75.9%. The study included 95 patients with COPD (30 women and 65 men). The mean age of patients was 54.2±1.4 years old, the duration of the disease was from 4 to 22 years old. A decrease in forced expiratory volume in 1 second was associated with a decrease in the density of bone tissue ($r = -0.86$, $p < 0.01$) [8]. Systemic inflammation in patients with COPD, associated with the development of interleukins IL-6, IL-1, IL-8, and TNF-α, stimulates osteoclast-mediated resorption of the bone tissue [9]. Apart from the specified anti-inflammatory cytokines, a lot of attention is paid to the factors that were united in the system of "osteoprotegerin (OPG) – receptor activator of nuclear factor kappa-B ligand" that regulate bone resorption in the norm and pathological condition [10].

OPG is a glycoprotein from the family of tumor necrosis factor (TNF) that is produced by the osteoblastic cells [11]. The mechanism of its action is in the neutralization of the receptor activator of nuclear factor kappa-B ligand (NF-kB)- RANKL. Thus, the interaction between the activator of NF-kB- RANK receptor and its RANKL ligand on the surface of pre-osteoclasts is blocked, which leads to the inhibition of the final stage of osteoclast differentiation and bone resorption [12]. In 43 out of 55 patients with COPD, osteopenic syndrome was diagnosed: the level of OPG in the serum was lower than in the control. An increase in the severity of COPD was characterized by a lower level of OPG. Besides, there was an inverse correlation between the level of TNF-α and myelin basic protein. At the same time, the content of TNF-α positively correlated with the level of β-CrossLaps [10].

β-CrossLaps are C-terminal telopeptides that are formed after the degradation of collagen type I that represents 90% of the organic matrix of bones. In the norm, minor fragments of collagen formed after bone degradation get into the bloodstream and are excreted with the kidneys. In patients with osteoporosis, collagen type I is destructed in great amounts, so the number of collagen fragments in the blood increases [13–14]. Patients with COPD have a sharp increase in the level of CrossLaps (CL-component of C-terminal telopeptide collagen type I) nearly by 3 times in comparison with the control group [8].

Markers of degradation are represented by a tartrate-resistant acid phosphatase (TRAP) (osteoclast-regulating protein) and free products of degradation of collagen type I: pyridolin (PYD), deoxypyridolin (DPD), N-terminal telopeptide, and cross-linked C-telopeptide [15].

TRAP from the family of acid phosphatases has been a cytochemical marker of osteoclast functioning since 1959 [16, 17]. Its effect is in the transcellular transport of microbubbles with the products of bone degradation [18–20]. Presently, there are five different forms of this enzyme.

They are produced by tissues (spleen, bone tissue, prostate) and cells (platelets, erythrocytes, macrophages). All five isoforms are suppressed by L(+)-tartrate, except for isoenzyme-5. There are two types of TRAP-5: 5α-containing sialic acid expressed by macrophages and 5β-containing acid that is synthesized only by osteoclasts, directly reflects their activity, and is measured by the colorimetric method [21, 22]. Besides, TRAP-5β dephosphorylates osteopontin and bone sialoprotein, disturbs their links with integrins $\alpha_v\beta_3$, and signals the end of resorption [21].

A molecule of bone collagen is stabilized by hydroxypyridine cross-links of PYD and DPD that are formed during the extracellular maturation of collagen [23]. During disorganization of the bone tissue, the cross-links get broken and their fragments get into the bloodstream and excreted with the urine [24, 25]. It should be mentioned that the level of cross-links reflects the degradation of only mature collagen and not newly formed, and the content of PYD and DPD does not depend on the character of the nutrition. PYD and PDP have a high affinity to skeletal tissues. Even though PYD is detected in the cartilaginous tissue, ligaments, and vessels, and DPD – primarily in the bone tissue and dentine, their presence indicates destruction of the bone tissue because the level of metabolism in bones is higher than in the above-mentioned tissues. Presently, the detection of these cross-links is possible by a highly-sensitive method of liquid chromatography with mass-spectrometry and a silicon dioxide column [26].

Radioimmunoassay is used for the evaluation of the level of amino and carboxyterminal telopeptides (NTX(NTP) and CTP(CTX), respectively) that are the terminal parts of a collagen molecule. CTP (CTX) have 4 isoforms (α-L form, β-isomeric peptide (β-L)), and α- and β- D-isomers. The measurement of NTX(NTP) is based on the evaluation of monoclonal bodies to antigen determinant of α-2 collagen chain. The identification of these forms provides information on the age-related changes in the metabolism of the skeleton of the healthy population and patients with connective tissue diseases [27].

Disorders in the formation of collagen in the bone tissue manifested as a decrease in the number of cross-links in collagen chains were revealed in *in vivo* and *in vitro* studies in patients with a high level of homocysteine [28]. The Hordaland Homocysteine Study [29] that included 2639 women and 2127 men aged 65 to 67 years old revealed an increase in the risk of femoral neck fractures in women with a high level of homocysteine (≥15 μM) in comparison with women with a low level (<9.0 μM). This is explained by the fact that hyperhomocysteinemia can be associated with a polymorphism of methylenetetrahydrofolate reductase, MTHFR (type C677T: TT), which exerts a negative effect on nervous, vascular, and endothelial cells, osteoblasts, and osteoclasts through an enhancement of the oxidative stress and increase in the level of the final products of glycation that lead to a decrease in the bone strength [30, 31].

It is difficult to underestimate the importance of vitamin D (VD) in the maintenance of adequate mineralization of bone tissue and skeleton formation. This vitamin regulates more than 2000 genes in a human organism [32]. In the skin, under the effect of ultraviolet light with wavelength 290–315 nm, Vitamin D3 is synthesized out of 7-dehydrocholesterol. In plants, vitamin D2 is synthesized through a modification of ergosterol. VD that gets absorbed with food and synthesized in the skin undergoes a series of transformations in the liver under the influence of 25-hydroxylase of mitochondria (CYP 27A1) and microsomes (CYP2R1) with the formation of calcidiol and ergocalcidiol. In the proximal sections of kidney tubules, these molecules turn into calcitriol and ergocalcitriol (active hormonal forms of VD). It was noted that the intensity of the formation of active forms directly depended on the level of protein that binds VD and albumin, which are synthesized in the liver and transport metabolites of VD. It can be concluded that disorders in the protein synthesizing function lead to a deficit of transport proteins, and as a result, to a deficit of VD and osteopenia [32, 33].

As it was mentioned before, the final stage of the activation of VD metabolites is performed in the kidneys. This process is catalyzed by a mitochondrial enzyme from a cytochrome P450 family 1α-hydroxylase (CYP 27B1). The activity of CYP 27B1 and synthesis of VD by the kidneys are stimulated by parathyroid hormone and insulin-like growth factor. The mechanisms of resistance to vitamin D depend on the level of 1α-hydroxylase because calcidiol converted by CYP 274B1 to calcitriol is required for the establishment of the links with the receptors of VD in the target organs for the formation of the gene response through the formation of X-receptor complex that induces the expression of calcium cationic canals in the intestinal epithelium [34].

The influence of a genetic factor in the development of a decreased bone density was studied by several authors [13, 34, 35, 36]. One of the gene candidates for the development of osteoporosis is a polymorphism of the gene receptor of vitamin D (VDR). This gene is localized in the chromosome 12q13.11 and contains a number of mononucleotide polymorphisms, including polymorphism Bsml. A total of 525 women in postmenopause were examined [35] (38–88 years old). The study [35] on the association of genotypes and alleles of polymorphism 283 A > G (Bsml) of the gene VDR showed that genotype GG or allele G of the polymorphism 283 A > G (Bsml) of the gene VDR was a predictor of osteoporosis of lumbar vertebra L1-L4. However, there was no association of this polymorphism with a decrease in the density of the bone tissue of the proximal section of femoral bones and the distal section of the antebrachium revealed. This discrepancy can be explained by the prevalence of the spongy material in the proximal sections of the femoral bones and distal sections of the antebrachium, and in the lumbar vertebra – trabecular substance.

Polymorphism of the gene receptor of calcitonin (CALCR) is also considered as a genetic predictor of osteoporosis [37]. Calcitonin is a hormone that is synthesized in the parafollicular cells of the thyroid body and regulates calcium and phosphorus metabolism in the organism. Bone tissue is a target organ for calcitonin and the inhibition of bone resorption is the main activity. CALCR occupies site 7q21.3 and codes the isoform-1 of a highly-sensitive receptor for calcitonin. A replacement of cytosine with thymine (C>T) in the exon 17 of the gene CALCR in position 1340 leads to a replacement of proline (CCG) with leucine (CTG) in position 463 in a molecule of protein receptor and influences the density of bones [38, 39]. It was established that allele C of the polymorphism of the gene CALCR leads to a decrease in the bone density, and the risk of osteoporosis depends on the physiological condition of the organism (adolescents, pregnant or lactating women) [37].

The genes of bone tissue remodeling also include the gene of lactase LCT (LPH) 13910 T>C and the gene of collage COL1A1 2046 G>T [36]. The function of the gene LCT (LPH) is the coding of the amino acid structure of the lactase that is synthesized in the small intestine and is necessary for lactose (milk sugar) splitting. Usually, this enzyme functions in children. In adults, it is not produced, which leads to intestinal disorders associated with lactose intolerance. Mutation in the site LCT (LPH) 13910 leads to a disturbance in the regulation of transcriptional activity of the lactase gene, while a normal variant of polymorphism C correlates with a decrease in the production of lactase in adults and a mutant T – with its maintenance. Thus, homozygotes in the allele C cannot digest lactose and homozygotes in the allele T can. Women in the post-menopausal period who have allele C are prone to osteoporosis and require a prescription of calcium-based drugs [36].

The role of COL1A1 is in the coding of protein sequence α1 of the collagen chain of type I. Multimorphism of COL1A1 is characterized by a replacement of guanine with thymine, which leads to disturbances in the site of binding for the factor of transcription in the area of the first intron. In patients with allele T (especially homozygote) of this polymorphism, idiopathic osteoporosis develops. Heterozygotes in the allele G/T have the lowest mineral density of bone tissue in comparison with homozygotes G/G [36]. Ninety-seven women with osteoporosis (49 Russians and 48 Buryats aged 50 to 80 years old) were studied. In the group of Buryat women, an accumulation of a recessive allele A of the gene VDR (Bsm1 c.IVS7G> A) was observed, which increased the risk of osteoporosis in individuals. Allele C of polymorphism (LCT) -13910 T>C was associated with the development of osteoporosis among Buryat women. When Buryat women had allele A in the gene VDR Bsm1 c.IVS7G> A and the allele C of lactase LCT -13910 T>C, they had a higher risk of the development of osteoporosis than Russian women. Genotypes G/T and T/T of the gene polymorphism COL1A 12046 G-> T were associated with the development of osteoporosis among the population of both nationalities.

However, a special role in the regulation of bone homeostasis is occupied by one of the most ancient phylogenetically formed mechanisms – Wnt, signaling pathway (SP-Wnt), which controls the bone tissue due to the influence on the process of differentiation of mesenchymal stem cells, stimulation of replication of pre-osteoblasts, inhibition of apoptosis of osteoblasts and osteocytes [40–42].

First, the role of SP-Wnt was mentioned in the regulation of the bone tissue density in 2001, when such an osteoporosis syndrome as pseudoglioma was revealed, which was characterized by a combination of a decrease in the mineral density of the bone tissue, retinal detachment, and cataract. This syndrome is inherited by an autosome-recessive type due to a mutation in the gene LRP5 in the 11th chromosome, which leads to a decrease in bone formation due to inhibition of SP-Wnt [43]. Mutation in the allele LRP5 can initiate the development of juvenile osteoporosis. The study included 235 Finnish men aged 18.3 to 20.6 years old. Only polymorphism A1330V LRP5 was significantly associated with the parameters of bones. In comparison with patients with genotype AlaAla (n = 215), patients with genotype AlaVal (n = 20) had the bone mineral content (BMC) of the lower part of the femoral neck P = 0.029 and bone mineral density (BMD) P = 0.012, BMC of trochanter P = 0.0067 and BMD P = 0.015, and general BMC of the femoral bone (P = 0.0044) and BMD (P = 0.0089) [44].

The antagonists of SP-Wnt also include one of the representatives of the DAN glycoprotein family (differential screening selected gene aberrant in neuroblastoma) – sclerostin [45]. Sclerostin is synthesized by osteocytes and binds with the receptor of lipoproteins of very low density 5 (LRP5; main membrane-associated cofactor of the Wnt-signal pathway) on their surface, as well as closely interacts with the coreceptor LRP6. Such interaction leads to SP-Wnt blocking and thus, the impossibility of osteoblastogenesis [46].

Specialists in practical healthcare need to be able to use and interpret the above-mentioned markers for the evaluation of the mineral density in patients with a predisposition to osteoporosis. During the past years, a lot of biochemical, molecular, and genetic factors have been studied in the development of osteoporosis. A special direction in these studies is the genetic regulation of bone remodeling. For this reason, this area is perspective in practical application for the diagnostics and treatment of osteoporosis.

Finansing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Шапорова Н.Л., Трофимов В.Н. Вторичный остеопороз у пациентов с хронической обструктивной патологией легких. // *Медицинский Совет*. – 2013. - №11. – С.54-57. DOI: 10.21518/2079-701X-2013-11-54-57
2. Исмаилов С.И., Ходжамбердиева Д.Ш., Рихсиева Н.Т. Остеопороз и низкоэнергетические переломы шейки бедра как осложнение различных эндокринных заболеваний. // *Международный эндокринологический журнал*. – 2013. – Т.5, №53. – С. 113-120. DOI: 10.22141/2224-0721.5.53.2013.84514.
3. Баранова И.А. Остеопороз в практике пульмонолога. // *Фарматека. Спецвыпуск: остеопороз*. – 2013. - s5-13. – С. 14—20. eLIBRARY ID: 21772795
4. Kanis J.A., Johnell O., Oden A., Johansson H., De Laet C., et al. Smoking and fracture risk: a meta-analysis // *Osteoporos. Int*. – 2005. – V.16(2). – P. 155-62. DOI: 10.1007/s00198-004-1640-3.
5. *Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Diagnosis and Treatment of Osteoporosis,* 5th edition. – July, 2006.
6. Slemeda C.W., Hui S. L. Longsope C., Johnston CC Jr. Cigarette smoking, obesity, and bone mass. // *J Bone Miner Res.* – 1989. – V.4(5). – P.737-41. DOI: 10.1002/jbmr.5650040513
7. Strozyk D., Gress T.M., Breitling L.P. Smoking and bone mineral density: comprehensive analyses of the third National Health and Nutrition Examination Survey (NHANES III). // *Arch Osteoporos.* – 2018. – V.13(1). – P.16. DOI: 10.1007/s11657-018-0426-8
8. Кочеткова Е.А., Волкова М.В., Петешова Е.Е., Гельцер Б.И. Патофизиологические аспекты пульмоногенных остеопений. // *Бюллетень физиологии и патологии дыхания*. – 2001. - №10. – С. 42-46. eLIBRARY ID: 9125737
9. Pennisi P., Signorelli S., Riccobene S., Celotta G., Di Pino L., et al. Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels // *Osteoporos. Int.* – 2004. – V.15. – P. 389–95. DOI: 10.1007/s00198-003-1550-9
10. Кочеткова Е. А., Буря К. А., Угай Л. Г., Коцюрбий Е. А., Невзорова В. А., и др. Роль остеопротегерина в формировании остеопенического синдрома при хронической обструктивной болезни легких. // *Тихоокеанский медицинский журнал*. – 2013. - №1ю – С. 20–22. eLIBRARY ID: 20191560
11. Юренева, С. В. Остеопротегерин и его лиганды в регуляции костной резорбции: экспериментальные и клинические аспекты применения при эстрогендефицитных состояниях. // *Журнал акушерства и женских болезней*. – 2004. – Т. 53, №1. – С.107-110. eLIBRARY ID: 9232027
12. Кочеткова Е.А., Невзорова В.А., Майстровская Ю.В., Массард Ж. Остеопротегерин и минеральная плотность костной ткани у пациентов с хронической обструктивной болезнью легких // *Терапевтический архив*. – 2010. – Т.82(8). – С.10-14. eLIBRARY ID: 15168307
13. Климова Ж.А., Зафт А.А., Зафт В.Б. Современная лабораторная диагностика остеопороза. // *Международный эндокринологический журнал*. – 2014. - № 7(63) – С. 74-84. DOI: 10.22141/2224-0721.7.63.2014.77130
14. Васильева Л.В., Евстратова Е.Ф., Никитин В.А., Латышева М.Н. Патогенетические механизмы лечения болевого синдрома в поясничной области, обусловленного остеопорозом смешанного генеза у больных хронической обструктивной болезнью легких. // *Фарматека*. – 2019. – Т.26, №5. – С. 92–96. DOI: 10.18565/pharmateca.2019.5.92-96.

REFERENCES

1. Shaporova N.L., Trofimov V.I. Secondary osteoporosis in patients with chronic obstructive lung disease. *Meditsinskiy sovet = Medical Council*. 2013;(11):54-57. (In Russ.) DOI: 10.21518/2079-701X-2013-11-54-57
2. Ismailov S.I., Khodjamberdiyeva D.Sh., Rikhsiyeva N.T. Osteoporosis and Low-energy Hip Fractures as Complication of Various Endocrine Diseases. *International journale of endocrinology*. 2013;5(53):113-120. (In Russ.). DOI: 10.22141/2224-0721.5.53.2013. 84514
3. Baranova I.A. Osteoporosis in practice of pulmonologist. *Pharmateka. Spetsvypusk: osteoporoz.* 2013;s5-13:14—20. (In Russ.). eLIBRARY ID: 21772795
4. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int.* 2005;16(2):155-62. DOI: 10.1007/s00198-004-1640-3
5. *Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Diagnosis and Treatment of Osteoporosis,* 5th edition. July, 2006.
6. Slemenda CW, Hui SL, Longcope C, Johnston CC Jr. Cigarette smoking, obesity, and bone mass. *J Bone Miner Res.* 1989;4(5):737-41. DOI: 10.1002/jbmr.5650040513
7. Strozyk D, Gress TM, Breitling LP. Smoking and bone mineral density: comprehensive analyses of the third National Health and Nutrition Examination Survey (NHANES III). *Arch Osteoporos.* 2018;13(1):16. DOI: 10.1007/s11657-018-0426-8
8. Kochetkova E.A., Volkova M.V., Peteshova E.E., Geltser B.I. Pathophysiological aspects pulmonology osteopenia. *Bulletin physiology and pathology of respiration.* 2001;(10):42-46. (In Russ.). eLIBRARY ID: 9125737
9. Pennisi P, Signorelli SS, Riccobene S, Celotta G, Di Pino L, et al. Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels. *Osteoporos Int.* 2004;15(5):389-95. doi: 10.1007/s00198-003-1550-9.
10. Kochetkova E. A., Bourya K. A., Ugay L. G., Kotsyubiy E. A., Nevzorova V. A., et al. Role of osteoprotegerin in the development of osteopenic syndrome in case of chronic obstructive lung disease. *Pacific Medical Journal*. 2013;1:20–22. (In Russ.). eLIBRARY ID: 20191560
11. Yureneva S.V. Osteoprotegerin and its ligands for regulating the osteal resorption: experimental and clinical application aspects under estrogen deficiency conditions. *Journal of Obstetrics and Women's Diseases*. 2004;53(1):107-110. (In Russ.). eLIBRARY ID: 9232027
12. Kochetkova E.A., Nevzorova V.A., Maĭstrovskaia Iu.V., Massard G. Osteoprotegerin and bone mineral density in patients with chronic obstructive pulmonary disease. *Terapevticheskii arkhiv*. 2010;82(8):10-14. (In Russ.). eLIBRARY ID: 15168307
13. Klimova Zh.A., Zaft A.A., Zaft V.B. Modern Laboratory Diagnosis of Osteoporosis. *International journale of endocrinology.* 2013;5(53):113-120. (In Russ.). DOI: 10.22141/2224-0721.7.63.2014.77130
14. Vasilyeva L.V., Evstratova E.F., Nikitin V.A., Latysheva M.N. Pathogenetic mechanisms for the treatment of the lumbar pain syndrome caused by osteoporosis of mixed genesis in patients with chronic obstructive pulmonary disease. *Pharmateka.* 2019;26(5):92–96. (In Russ.). DOI: 10.18565/pharmateca.2019.5.92-96
15. Pobel E.A., Bengus L.M., Dedukh N.V. Markers of bone metabolism in long bone's adhesion. *Osteoporosis and osteopathy*. 2012;15(2):25–32. (In Russ.). eLIBRARY ID: 18875416
16. Smirnov A. V., Rumyantsev A. Sh. Bone tissue function and structure under normal and pathological conditions. Message I. *Nephrology*. 2014;18(6):9-25. (In Russ.). eLIBRARY ID: 22703984

15. Побел Е.А., Бенгус Л.М., Дедух Н.В. Маркеры костного метаболизма при сращении переломов длинных костей. // *Остеопороз и остеопатии*. - 2012. – Т. 15, №2. – С.25–32. eLIBRARY ID: 18875416
16. Смирнов А. В., Румянцев А. Ш. Строение и функции костной ткани в норме и при патологии. Сообщение I. // *Нефрология*. – 2014. - Т.18, №6. – С.9–25. eLIBRARY ID: 22703984
17. Burstone M.S. Histochemical demonstration of acid phosphatase activity in osteoclasts. // *J Histochem Cytochem*. – 1959. – V.7(1). – P.39-41. DOI: 10.1177/7.1.39
18. Clarke B. Normal bone anatomy and physiology. // *Clin J Am Soc Nephrol*. – 2008. –V.3 Suppl 3. – P.S131-139. DOI: 10.2215/CJN.04151206.
19. Tolar J., Teitelbaum S.L, Orchard P.J. Osteopetrosis. // *N Engl J Med*. – 2004. – V.351(27). – P. 2839-2849. DOI: 10.1056/NEJMra040952.
20. Москалец А.И., Бондарук О.С., Щербина О.В. Маркеры костного метаболизма и их роль в клинической практике // *Лабораторная диагностика*. - 2012. - № 1 (59). - С. 67-72.
21. Halleen J.M., Alatalo S.L., Suominen H., Cheng S., Janckila A.J., Vaananen H.K. Tartrate-resistant acid phosphatase 5b: a novelserum marker of bone resorption // *J. Bone Miner. Res.* - 2000. - V. 15. - P. 1337–1345. DOI: 10.1359/jbmr.2000.15.7.1337
22. Halleen J.M., Karp M., Viloma S., Laaksonen P., Hellman J., et al. Two-site immunoassays for osteoclastic tartrate-resistant acid phosphatase based on characterisation of six monoclonal antibodies // *J. Bone Miner. Res*. - 1999. - V. 14. - P. 464–469. DOI: 10.1359/jbmr.1999.14.3.464
23. Van der Mark K., Seibel M, Robins S, Bilezikian J eds. *Structure and biosynthesis of collagens. in: dynamics of bone and car tilage metabolism*. - San Diego: Academic Press, 1999.
24. Delmas P.D., Schlemmer A., Gineyts E., Riis B., Christiansen C. Urinary excretion of pyridinoline crosslinks correlates with bone turnover measured on iliac crest biopsy in patients with vertebral osteoporosis // *J. Bone Miner. Res*. - 1991. - V. 6. - P. 639– 644. DOI: 10.1002/jbmr.5650060615
25. Eastell R., Colwell A., Hampton L., Reeve J. Biochemical markers of bone resorption compared with estimates of bone resorption from radiotracer kinetic studies in osteoporosis // *J. Bone Miner. Res.* - 1997. - V. 12. - P. 59–65. DOI: 10.1359/jbmr.1997.12.1.59
26. Naffa R., Watanabe S., Zhang W., Maidment C., Singh P., et al. Rapid analysis of pyridinoline and deoxypyridinoline in biological samples by liquid chromatography with mass spectrometry and a silica hydride column. // *J Sep Sci.* – 2019. – V. 42(8). – P. 1482-1488. DOI: 10.1002/jssc.201801292.
27. Hanson D.A., Weis M.A., Bollen A.M., Maslan S.L.,Singer F.R., Eyre D.R. A specific immunoassay for monitoring human bone resorption: quantitation of type I collagen cross-linked N-telopeptides in urine // *J Bone Miner Res.* – 1992. – V.7(11). – P. 1251-1258. DOI: 10.1002/jbmr.5650071119.
28. Dhonukshe-Rutten R.A., Pluijm S.M., de Groot L.C., Lips P, Smit J.H., van Staveren W.A. Homocysteine and vitamin B12 status relate to bone turnover markers, broadband ultrasound attenuation, and fractures in healthy elderly people. // *J Bone Miner Res*. – 2005. – V.20(6). – P. 921-9. DOI: 10.1359/JBMR.050202.
29. Gjesdal C.G., Vollset S.E., Ueland P.M., Refsum H., Meyer H.E., Tell G.S. Plasma homocysteine, folate, and vitamin B 12 and the risk of hip fracture: the hordaland homocysteine study. // *J Bone Miner Res*. – 2007. – V.22(5). – P. 747-56. DOI: 10.1359/jbmr.070210.
30. Saito M., Marumo K. The Effects of Homocysteine on the Skeleton. // *Curr Osteoporos Rep*. – 2018. – V. 16(5). – P.554-560. DOI: 10.1007/s11914-018-0469-1.
17. Burstone MS. Histochemical demonstration of acid phosphatase activity in osteoclasts. *J Histochem Cytochem.* 1959;7(1):39-41. DOI: 10.1177/7.1.39
18. Clarke B. Normal bone anatomy and physiology. // *Clin J Am Soc Nephrol*. 2008;3 Suppl 3:S131-139. DOI: 10.2215/CJN.04151206.
19. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. *N Engl J Med*. 2004;351(27):2839-49. DOI: 10.1056/NEJMra040952
20. Moskalets A.I., Bondaruk O.S., Shcherbina O.V. Markers of bone metabolism and their role in clinical practice. *Laboratory diagnostics.* 2012;1(59):67-72. (In Russ.).
21. Halleen JM, Alatalo SL, Suominen H, Cheng S, Janckila AJ, Väänänen HK. Tartrate-resistant acid phosphatase 5b: a novel serum marker of bone resorption. *J Bone Miner Res.* 2000;15(7):1337-45. DOI: 10.1359/jbmr.2000.15.7.1337
22. Halleen JM, Karp M, Viloma S, Laaksonen P, Hellman J, et al. Two-site immunoassays for osteoclastic tartrate-resistant acid phosphatase based on characterization of six monoclonal antibodies. *J Bone Miner Res.* 1999;14(3):464-9. DOI: 10.1359/jbmr.1999.14.3.464
23. Van der Mark K., Seibel M, Robins S, Bilezikian J eds. *Structure and biosynthesis of collagens. in: dynamics of bone and car tilage metabolism.* San Diego: Academic Press, 1999.
24. Delmas PD, Schlemmer A, Gineyts E, Riis B, Christiansen C. Urinary excretion of pyridinoline crosslinks correlates with bone turnover measured on iliac crest biopsy in patients with vertebral osteoporosis. *J Bone Miner Res.* 1991;6(6):639-44. DOI: 10.1002/jbmr.5650060615
25. Eastell R, Colwell A, Hampton L, Reeve J. Biochemical markers of bone resorption compared with estimates of bone resorption from radiotracer kinetic studies in osteoporosis. *J Bone Miner Res.* 1997 Jan;12(1):59-65. DOI: 10.1359/jbmr.1997.12.1.59
26. Naffa R., Watanabe S., Zhang W., Maidment C., Singh P., et al. Rapid analysis of pyridinoline and deoxypyridinoline in biological samples by liquid chromatography with mass spectrometry and a silica hydride column. *J Sep Sci.* 2019;42(8):1482-1488. DOI: 10.1002/jssc.201801292.
27. Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR. A specific immunoassay for monitoring human bone resorption: quantitation of type I collagen cross-linked N-telopeptides in urine. *J Bone Miner Res.* 1992;7(11):1251-8. DOI: 10.1002/jbmr.5650071119
28. Dhonukshe-Rutten RA, Pluijm SM, de Groot LC, Lips P, Smit JH, van Staveren WA. Homocysteine and vitamin B12 status relate to bone turnover markers, broadband ultrasound attenuation, and fractures in healthy elderly people. *J Bone Miner Res.* 2005;20(6):921-9. DOI: 10.1359/JBMR.050202
29. Gjesdal CG, Vollset SE, Ueland PM, Refsum H, Meyer HE, Tell GS. Plasma homocysteine, folate, and vitamin B 12 and the risk of hip fracture: the hordaland homocysteine study. *J Bone Miner Res.* 2007;22(5):747-56. DOI: 10.1359/jbmr.070210
30. Saito M, Marumo K. The Effects of Homocysteine on the Skeleton. *Curr Osteoporos Rep*. 2018;16(5):554-560. DOI: 10.1007/s11914-018-0469-1
31. Zaric BL, Obradovic M, Bajic V, Haidara MA, Jovanovic M, Isenovic ER. Homocysteine and Hyperhomocysteinaemia. *Curr Med Chem*. 2019;26(16):2948-2961. DOI: 10.2174/0929867325666180313105949
32. Maylyan E.A., Rheznichenko N.A., Maylyan D.E. Vitamin D regulation of bone metabolism. *Medical Herald of the South of Russia*. 2017;(1):12-20. (In Russ.) DOi: 10.21886/2219-8075-2017-1-12-20

31. Zaric B.L., Obradovic M., Bajic V., Haidara M.A., Jovanovic M., Isenovic E.R. Homocysteine and Hyperhomocysteinaemia. // *Curr Med Chem*. – 2019. – V.26(16). – P.2948-2961. DOI: 10.2174/0929867325666180313105949.
32. Майлян Э.А., Резниченко Н.А., Майлян Д.Э. Регуляция витамином D метаболизма костной ткани. // *Медицинский вестник Юга России*. – 2017. - №1. – С.12-20. DOI: 10.21886/2219-8075-2017-1-12-20.
33. Мальцев С.В., Мансурова Г.Ш. Метаболизм витамина D и пути реализации его основных функций. // *Практическая медицина*. – 2014. - №9(85). – С.12-19. eLIBRARY ID: 22597066
34. Яковлева О.А., Николова О.М., Дорошкевич И.А., Щербенюк Н.В. Генетический полиморфизм рецептора витамина D определяет его метаболизм и эффективность. // *Боль. Суставы. Позвоночник*. – 2017. – Т.7, №2. – С. 73-78. DOI: 10.22141/2224-1507.7.2.2017.108699.
35. Майлян Э.А. Влияние полиморфизма 283 A>G (BSMI) гена рецептора витамина D на развитие остеопороза у женщин в постменопаузе. // *Медицинский вестник Юга России*. – 2016. - №4. – С.32-38. DOI: 10.21886/2219-8075-2016-4-32-38.
36. Верхотурова С.В., Царенок С.Ю., Горбунов В.В., Аксенова Т.А. Полиморфизм некоторых генов метаболизма костной ткани (VDR BSM1 C.IVS7G >A, LCT 13910 T>C, COL1A 12046 G->T) у представительниц русской и бурятской национальностей. // *Остеопороз и остеопатии*. – 2017. – Т.20, №1. – С. 3-6. DOI: 10.14341/osteo201713-6.
37. Шилина Н.М., Сорокина Е.Ю., Иванушкина Т.А., Сафронова А.И., Гмошинская М.В., Конь И.Я. Изучение полиморфизма rs11801197 гена рецептора кальцитонина (CALCR) у женщин и детей Москвы с различным уровнем костной прочности. // *Вопр. питания*. – 2017. – Т.86, №1. – С.28–33. DOI: 10.24411/0042-8833-2017-00017.
38. Masi L., Becherini L., Gennari L., Colli E., Mansani R., et al. Allelic variants of human calcitonin receptor: distribution and association with bone mass in postmenopausal Italian women. // *Biochem Biophys Res Commun*. – 1998. – V.245 (2). – P. 622–6. DOI: 10.1006/bbrc.1998.8445
39. Nakamura M., Zhang Z., Shan L., Hisa T., Sasaki M., et al. Allelic variants of human calcitonin receptor in the Japanese population. // *Hum Genet*. – 1997. – V.99 (1). – P. 38–41. DOI: 10.1007/s004390050307
40. Day T.F., Guo X., Garrett-Beal L., Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast an chondrocyte differentiation uring vertebrate skeletogenesis. // *Dev Cell*. – 2005. – V.8(5). – P.739-750. DOI: 10.1016/j.devcel.2005.03.016
41. Rodda SJ, McMahon AP. Distinct roles for Hedgehog and canonical Wnt signaling in specification, differentiation and maintenance of osteoblast progenitors. // *Development*. – 2006. – V.133(16). – P. 3231-3244. DOI: 10.1242/dev.02480.
42. Гребенникова Т.А., Белая Ж.Е., Рожинская Л.Я., Мельниченко Г.А. Канонический сигнальный путь Wnt/β-катенин: от истории открытия до клинического применения. // *Терапевтический архив*. – 2016. – т. 88. – №10. – с. 74–81. DOI: 10.17116/terarkh201688674-81.
43. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, et. al; Osteoporosis-Pseudoglioma Syndrome Collaborative Group. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. // *Cell*. – 2001. – V. 107(4). – P. 513-523. DOI: 10.1016/s0092-8674(01)00571-2.
44. Saarinen A, Välimäki VV, Välimäki MJ, Löyttyniemi E, Auro K, et al. The A1330V polymorphism of the low-density lipoprotein receptor-related protein 5 gene (LRP5) associates with low peak bone mass in young healthy men. // *Bone*. – 2007. – V.40(4). – P. 1006-1012. DOI: 10.1016/j.bone.2006.11.010.
33. Malcev S.V., Mansurova G.Sh. The metabolism of vitamin D and the realization of its main functions. *Practical medicine Prakticheskaja medicina*. 2014;9(85):12-19. (In Russ.). eLIBRARY ID: 22597066
34. Yakovleva O.A., Nikolova O.M., Doroshkevych I.A., Shcherbeniuk N.V. Genetic polymorphism of vitamin D receptor determines its metabolism and efficiency. *Bol', Sustavy, Pozvonochnik*.2017;7(2):73-78. (In Russ.). DOI: 10.22141/2224-1507.7.2.2017.108699
35. Maylyan E.A. The influence of vitamin D receptor Gen 283 A>G (BSMI) polymorphism on osteoporosis in postmenopausal women. *Medical Herald of the South of Russia*. 2016;(4):32-38. (In Russ.) DOI: 10.21886/2219-8075-2016-4-32-38
36. Verkhoturova S.V., Tsarenok S.U., Gorbunov V.V., Aksenova T.A. Polymorphism of some genes of bone tissue metabolism (VDR Bsm1 c.IVS7G>A, LCT 13910 T>C, COL1A 12046 G->T) among the representatives of Russian and Buryat nationalities. *Osteoporosis and Bone Diseases*. 2017;20(1):3-6. (In Russ.) DOI: 10.14341/osteo201713-6
37. Shilina NM, Sorokina EY, Ivanushkina TA, Gmoshinskaya MV, Safronova AI, Kon' IY. [The study of rs11801197 polymorphism of the calcitonin receptor gene (CALCR) in Moscow women and children with different level of bone strength]. *Vopr Pitan*. 2017;86(1):28-34. (In Russ.) DOI: 10.24411/0042-8833-2017-00017
38. Masi L, Becherini L, Gennari L, Colli E, Mansani R, et al. Allelic variants of human calcitonin receptor: distribution and association with bone mass in postmenopausal Italian women. *Biochem Biophys Res Commun*. 1998;245(2):622-6. DOI: 10.1006/bbrc.1998.8445
39. Nakamura M, Zhang ZQ, Shan L, Hisa T, Sasaki M, et al. Allelic variants of human calcitonin receptor in the Japanese population. *Hum Genet*. 1997;99(1):38-41. DOI: 10.1007/s004390050307
40. Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell*. 2005;8(5):739-50. DOI: 10.1016/j.devcel.2005.03.016
41. Rodda SJ, McMahon AP. Distinct roles for Hedgehog and canonical Wnt signaling in specification, differentiation and maintenance of osteoblast progenitors. *Development*. 2006;133(16):3231-44. DOI: 10.1242/dev.02480
42. Grebennikova TA, Belaya ZE, Rozhinskaya LY, Melnichenko GA. Kanonicheskiĭ signal'nyĭ put' Wnt/β-katenin: ot istorii otkrytiia do klinicheskogo primeneniia [The canonical Wnt/β-catenin pathway: From the history of its discovery to clinical application]. *Ter Arkh*. 2016;88(10):74-81. (In Russ.) DOI: 10.17116/terarkh201688674-81
43. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell*. 2001;107(4):513-23. DOI: 10.1016/s0092-8674(01)00571-2
44. Saarinen A, Välimäki VV, Välimäki MJ, Löyttyniemi E, Auro K, et al. The A1330V polymorphism of the low-density lipoprotein receptor-related protein 5 gene (LRP5) associates with low peak bone mass in young healthy men. *Bone*. 2007;40(4):1006-12. DOI: 10.1016/j.bone.2006.11.010
45. Dydykina I.S., Vetkova E.S. Sclerostin and its role in the regulation of bone metabolism. *Rheumatology Science and Practice*. 2013;51(3):296-301. (In Russ.) DOI: 10.14412/1995-4484-2013-1505
46. van Bezooijen RL, Roelen BA, Visser A, van der Wee-Pals L, de Wilt E, et al. Sclerostin is an osteocyte-expressed nega-

45. Дыдыкина И.С., Веткова Е.С. Склеростин и его роль в регуляции метаболизма костной ткани. // *Научно-практическая ревматология*. – 2013. – Т.51, №3. – С.296-301. DOI: 10.14412/1995-4484-2013-1505.
46. Van Bezooijen R.L., Roelen B.A., Visser A., van der Wee-Pals L., de Wilt E., et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but nota classical BMP antagonist. // *J Exper Med.* – 2004. – V. 199. – P. 805–14. DOI: 10.1084/jem.20031454.

tive regulator of bone formation, but not a classical BMP antagonist. *J Exp Med.* 2004;199(6):805-14. DOI: 10.1084/jem.20031454

Информация об авторах

Васильева Людмила Валентиновна, д.м.н., проф., заведующий кафедрой пропедевтики внутренних болезней, Воронежский государственный медицинский университет им. Н.Н. Бурденко, Воронеж, Россия. ORCID: 0000-0002-9900-556X. E-mail: propedevtikavgmu@mail.ru.

Беззубцева Екатерина Николаевна, аспирант 1 года обучения, кафедра пропедевтики внутренних болезней, Воронежский государственный медицинский университет им. Н.Н. Бурденко, Воронеж, Россия. ORCID: 0000-0003-0132-7841. E-mail: bezzubtsewa.ekaterina@yandex.ru.

Гостева Елена Владимировна, к.м.н., доцент, кафедра пропедевтики внутренних болезней, Воронежский государственный медицинский университет им. Н.Н. Бурденко, Воронеж, Россия. E-mail: propedevtikavgmu@mail.ru.

Евстратова Елизавета Федоровна, д.м.н., доц., кафедра пропедевтики внутренних болезней, Воронежский государственный медицинский университет им. Н.Н. Бурденко, Воронеж, Россия. ORCID: 0000-0001-9343-6222. E-mail: elizavet-evstratov@yandex.ru

Information about the authors

Ludmila V. Vasilyeva, Dr. Sci. (Med.), Therapist, Head of the Department of Propedeutics of Internal Diseases, N.N. Burdenko Voronezh State Medical University, Voronezh, Russia. ORCID: 0000-0002-9900-556X. E-mail: propedevtikavgmu@mail.ru.

Ekaterina N. Bezzubtseva, Post-graduate student of the Department of Propedeutics of Internal Diseases, N.N. Burdenko Voronezh State Medical University, Voronezh, Russia. ORCID: 0000-0003-0132-7841. E-mail: bezzubtsewa.ekaterina@yandex.ru.

Elena V. Gosteva, Cand. Sci. (Med), Associate Professor of the Department of Propedeutics of Internal Diseases, N.N. Burdenko Voronezh State Medical University, Voronezh, Russia. E-mail: propedevtikavgmu@mail.ru.

Eliveta F. Evstratova, Dr. Sci. (Med.), Associate Professor of the Department of Propedeutics of Internal Diseases, N.N. Burdenko Voronezh State Medical University, Voronezh, Russia. ORCID: 0000-0001-9343-6222. E-mail: elizavet-evstratov@yandex.ru

Вклад авторов

Васильева Л.В. — дизайн, написание, редактирование текста и утверждение финального варианта статьи;

Беззубцева Е.Н. — поиск литературных источников, написание текста, редактирование;

Гостева Е.В. — редактирование текста и утверждение финального варианта статьи;

Евстратова Е.Ф. — редактирование текста и утверждение финального варианта статьи.

Authors contribution

Vasilyeva L.V. — design, writing, editing and approval of the final version of the article;

Bezzubtseva E.N. — search for literature, writing and editing the article;

Gosteva E.V. — editing and approval of the final version of the article;

Evstratova E.F. — editing and approval of the final version of the article.

Получено / Recived: 26.01.2021
Принято к печати / Accepted: 01.03.2021

УДК: 616.98:578:614.4
DOI 10.21886/2219-8075-2021-12-1-14-23

Human coronaviruses that can cause emergencies

A.A. Kononenko[1], A.K. Noskov[1], S.Yu. Vodyanitskaya[2], O.A. Podoynitsyna[1]

[1]Rostov-on-Don Anti-Plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia
[2]Ministry of health of the Rostov Region, Rostov-on-Don, Russia

The first coronavirus NCoV-B814 was isolated from humans in 1965 and did not survive to the present time. For a long time, it was believed that coronaviruses were not pathogenic to humans. They were not included in the list of particularly dangerous infections and represented a serious problem exclusively in veterinary medicine. But in 2002, after the SARS outbreak, scientists' opinions changed. A new subtype of the coronavirus called SARS-CoV penetrated the human population. In 2012, it was possible to discover natural foci of Middle East Respiratory Syndrome. The epidemic of a new coronavirus infection that emerged in late 2019 and early 2020 attracted the attention of scientists around the world. The priority was a detailed and close study of all the varieties of this virus. This review describes seven types of coronaviruses that can cause emergencies in populations around the world.

Keywords: human coronaviruses, HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, SARS-CoV-2, epidemic.

For citation: Kononenko A.A., Noskov A.K., Vodyanitskaya S.Yu., Podoynitsyna O.A. Human coronaviruses that can cause emergencies. *Medical Herald of the South of Russia.* 2021;12(1):14-23. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-14-23.

Corresponding author: Anna A. Kononenko, anna270391@yandex.ru.

Коронавирусы человека, способные вызывать чрезвычайные ситуации

А.А. Кононенко[1], А.К. Носков[1], С.Ю. Водяницкая[2], О.А. Подойницына[1]

[1]Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия
[2]Министерство здравоохранения Ростовской области, Ростов-на-Дону, Россия

Первый коронавирус HCoV-B814, выделенный от человека, был изолирован в 1965 г. и не сохранился до наших дней. Долгое время считалось, что коронавирусы не способны вызывать опасные для жизни заболевания. Они не входили в список особо опасных инфекций, а серьёзную проблему представляли исключительно в ветеринарии. Но с 2002 г., после вспышки тяжёлого острого респираторного синдрома, мнение ученых изменилось. Новый подтип коронавируса проник в популяцию людей и получил название SARS-CoV. В 2012 г. удалось открыть природные очаги Ближневосточного респираторного синдрома. Возникшая в конце 2019 г. эпидемия новой коронавирусной инфекции привлекла к себе внимание исследователей всего мира. Первоочередной задачей стало подробное и пристальное изучение всех разновидностей данного вируса. В данном обзоре описаны семь видов коронавирусов, способных вызывать чрезвычайные ситуации среди населения всего мира.

Ключевые слова: короновирусы человека, HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, SARS-CoV-2, эпидемия.

Для цитирования: Кононенко А.А., Носков А.К., Водяницкая С.Ю., Подойницына О.А. Коронавирусы человека, способные вызывать чрезвычайные ситуации. *Медицинский вестник Юга России.* 2021;12(1):14-23. DOI 10.21886/2219-8075-2021-12-1-14-23.

Контактное лицо: Анна Александровна Кононенко, anna270391@yandex.ru.

In the 1930s, after numerous studies, coronaviruses were officially acknowledged pathogenic for animals. Thirty years after, the strains were identified that caused respiratory diseases in humans [1].

Presently, coronaviruses form the largest group of the order *Nidovirales* that includes such families as *Coronaviridae, Arteriviridae, Roniviridae,* and *Mesoviridae*. The *Coronaviridae* family consists of two subfamilies *Coronavirinae* and *Torovirinae*. Coronaviruses are divided into 4 genera: *Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses,* and *Deltacoronaviruses*. Initially, within the genus *Betacoronavirus,* the viruses were divided into lines A, B, C, and D that were later renamed *Embecovirus* (previous line A), *Sarbecovirus* (previous line B), *Merbecovirus* (previous line C), and *Nobecovirus* (previous line D) [2]. These 4 lines are classified into subgenera of *Betacoronaviruses*.

Among numerous representatives of the family, seven coronaviruses can cause diseases in humans (Table 1). Four viruses (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-KHU1) are etiologic agents of acute respiratory viral infections (ARVIs) of light or moderate severity. Two viruses are capable of causing lethal diseases: severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV). The 7th virus (SARS-CoV-2) is a novel coronavirus. The first case of infection was registered in China at the end of 2019. At the beginning of 2020, SARS-CoV-2 spread all over the world [3, 4].

Human coronaviruses HCoV-229E and HCoV-OC43

In 1965, Tyrrell and Bynoe were the first to cultivate the virus that was isolated from the respiratory tract of a boy with regular cold by means of passage in the embryonal cultures of the organs of the human trachea [5, 6]. The first official scientific publication dedicated to coronaviruses is dated November 16,1968 in the journal *Nature*. It was proposed in the article to unite these viruses into a group of "*coronaviruses*" because of a typical morphology of virions 229E and OC43 with a precisely expressed corona-like enclosure (20 nm) of roundish pleiomorphic particles (120–160 nm) [7].

By a degree of pathogenicity, *Coronaviridae* were classified as

- Group IV of pathogenicity that included HCoV-229E and numerous animal viruses;
- Group III of pathogenicity that included viruses HCoV-OC43 and closely related animal viruses [6].

According to the official data obtained from different studies on volunteers included in the "healthy group", it was established that viruses HCoV-229E and HCoV-OC43 caused a regular cold [8, 9]. Since then, HCoVs were considered relatively pathogenic respiratory viruses.

It was proved experimentally that HCoV-229E and HCoV-OC43 were characterized by droplet transmission. Volunteers infected with this virus produced it within 5 days starting 48 hours after

Table 1 / Таблица

Classification of Coronavirinae viruses
Классификация вирусов Coronavirinae

Подсемейство/ *Subfamily*	Род/ *gender*	Подрод/ *Subgenus*	Линия/ *Line*	Вирусы/ *Viruses*	Код по МКБ-10/ *Code according to ICD-10*
Coronavirinae	*Alphacoronaviruses*	*Duvinacovirus*		HCoV-229E	
		Setracovirus		HCoV-NL63	
	Betacoronaviruses	*Embecovirus*	A	HCoV-OC43	
			A	HCoV-HKU1	
		Sarbecovirus	B	SARS-CoV	U04 Тяжёлый острый респираторный синдром *U04 Severe Acute Respiratory Syndrome*
			B	SARS-CoV-2	U07.1 COVID-19, вирус идентифицирован *U07. 1 COVID-19, virus identified*
		Merbecovirus	C	MERS-CoV	
	Gammacoronaviruses				
	Deltacoronaviruses				

infecting, which corresponded to the appearance of the first symptoms of the disease [10].

The studies showed that infection HCoV-229E was performed by the inoculation of the mucous membranes of the respiratory tract. The exudation of plasma of the nasal mucosa and increased levels of interferons γ (IFNy) in the samples of nasopharyngeal lavage directly depended on the severity of symptoms [11].

The viral load of the respiratory tract reached its maximum within the first three days after the infection and sharply decreased one week later, which was associated with the appearance of acquired active immunity in humans [12].

Starting from 2000, representatives of the *Coronaviridae* family were revealed that caused severe respiratory diseases that could result in a lethal outcome.

Human coronavirus SARS-CoV

The first case of the disease caused by SARS-CoV was registered in Shanlan, Guangdong province, in the south of China in November 2002. The transmission of the infection primarily occurred in hospital conditions. On average, one infected patient infected 3–4 people that they contacted. Italian doctor Carlo Urbani, who was a member of "Doctors Without Borders", was the first to identify the observed disease as novel. Carlo Urbani got infected during the treatment of a patient with SARS and died. The strain of the isolated virus was called after this doctor SARS-related human coronavirus Urbani (SARS). Due to Carlo Urbani and his colleagues' activities, it was possible to stop the spread of SARS [4].

In 2003, it was shown that the infecting agent of the disease was an earlier unknown variant of coronavirus. It was named SARS–CoV. Its genome organization was similar to coronavirus. However, phylogenetic analysis and comparison of the sequences suggested that SARS–CoV was not related to any of the viruses described before. Its virions contained a plus-strand of polyadenylated RNA 16–30 kb long (coronaviruses have the largest genome that threefold exceeds the genome of other viruses) [13]. SARS-CoV was classified as Group III pathogenicity accepted in the Russian Federation.

Based on the conducted studies, a hypothesis was made in the primary penetration of the virus into the human population when they ate civet meat because coronavirus isolated from these animals was inactivated by the blood serum of patients with SARS-CoV [14, 15].

Further, it was established that natural foci of SARS-CoV virus were associated with the habitats of Chiroptera, primarily, bats. Besides, SARS-CoV-like viruses were isolated from horseshoe bats *Rhinolophus* and species that belonged to other genera found in Asia (primarily, China), Africa, Australia, Europe, and the USA. It is impossible to exclude direct transmission of the infection to humans via the wastes of bats that can live in the attics of living facilities [3, 16].

The severity of the disease varied from a light to severe form with a lethal outcome. In the majority of patients, the disease developed to a light or moderate degree with signs of regular ARVI, quick recovery, and specific immunity. However, some patients developed a severe form of pneumonia, associated with severe acute respiratory syndrome [17, 18].

The spread of the disease was stopped in 2003 by highly effective global measures taken by the systems of healthcare worldwide. Presently, SARS does not circulate among the human population [19, 20].

As it was noted above, coronaviruses are capable of evolving and adapting to new hosts. The outburst of atypical pneumonia returned coronaviruses to the center of researchers' attention. As a result, two more representatives of the *Coronaviridae* family that could cause diseases in humans were isolated.

Human coronaviruses HCoV-NL63 and HCoV-HKU1

In 2004, Dutch scientists in the Netherlands were the first to isolate a novel virus HCoV-NL63 (Human coronavirus NL63) from a seven-month-old child with bronchiolitis. This virus was classified as Group IV of pathogenicity [21–23].

In January 2005, researchers from the University of Hong Kong isolated a novel human coronavirus HKU1 (HCoV-HKU1 — Human coronavirus HKU1) from a 71-year-old patient with acute respiratory disease complicated with bilateral pneumonia [24]. Hong Kong University introduced the prefix HKU in the classification of coronaviruses with a number of the strain that is met in the names of numerous viruses. HCoV-HKU1 virus was classified as Group III of pathogenicity.

HCoV-NL63 and HCoV-HKU1 are one-strand positive RNA viruses. The majority of patients had such symptoms as rhinorrhea, fever, cough, and hissing respiration. The disease manifestations included bronchitis and pneumonia [25, 26].

The first cases of infection of people with HCoV-NL63 were registered among infants with a severe infection of the lower respiratory tract in the inpatient conditions, while the first cases of HCoV-HKU1 infection were registered among senior patients with the main comorbid diseases of the respiratory and

cardiovascular systems. Presently, HCoV-HKU1 is also registered in children with acute respiratory diseases and infections of the upper or lower respiratory tracts [21, 26].

As a rule, diseases caused by HCoV-HKU1 and HCoV-NL63 viruses are not life-threatening, especially, for healthy people. It was suggested that HCoV-NL63 and HCoV-HKU1, as well as HCoV-229E and HCoV-OC43, are capable to provoke diseases with expressed clinical symptoms only in children, senior people, and those who have immune disorders [27].

From 2006 to 2012, coronaviruses were actively studied. In June 2012, a new representative of this family was isolated, which was called MERS-CoV.

Human coronavirus MERS-CoV

In June 2012, in Jidda (Saudi Arabia), a virologist Ali Mohamed Zaki isolated a novel coronavirus from the sputum of a patient who died because of severe viral pneumonia complicated by an acute kidney injury. By many signs, the virus was close to SARS-CoV. Thus, the novel infection was called Middle East respiratory syndrome.

Initially, the virus MERS-CoV was planned to be called a "virus of acute respiratory syndrome with kidney injury" but it was soon revealed that kidney injury was not a leading pathology, so for some time, the term "novel coronavirus" (HCoV-EMC/2012) was used. In May 2013, the virus was called MERS-CoV by the International Committee on Viral Taxonomy [28].

Even though the transmission of a virus between people was not intensive, MERS-CoV caused two major outbursts in Saudi Arabia (2012) and South Korea (in 2015), wherein the general number of confirmed cases exceeded two thousand at the level of lethality 35% [29]. In senior patients, especially those who had comorbid pathology, the infection caused by MERS-CoV had a sore severe development and often had a lethal outcome [28].

The virus MERS-CoV is a linear non-segmented one-strand positive RNA. By the degree of pathogenicity, the virus was classified as Group II by the classification accepted in the Russian Federation.

It was suggested that bats could be not the only reservoir of MERS-CoV. Some data confirmed the possibility of carriership in *Erinaceus europaeus*. Besides, it is possible that camels can host MERS-CoV [30].

It was established that MERS-CoV strains isolated from camels were completely identical to the strains isolated from humans. Besides, antibodies specific to MERS-CoV were often found in the samples of serum obtained from camels from the Middle East, Africa, and Asia collected in 1983. This, it is suggested that viruses circulate in the blood of camels for more than 30 years.

Numerous studies officially confirmed that the natural reservoir for MERS-CoV is a bat (Chiroptera). The virus isolated from one of the patients was identical in the molecular-genetic aspect to the virus isolated from pouched bats (*Taphozous perforatus*) from the family of shelf-tailed bats (Emballonuridae) [31]. Bats expressed virus with saliva, urine, and feces, that could become the source of infection for humans and other animals. Pouched bats were met not only in the south of the Arabian Peninsula but also in the western part of the Hindustan peninsula. Thus, it cannot be excluded that the areas of natural foci of MERS-CoV were wider than it was believed. It was shown that MERS-CoV was capable to reproduce in the primary cellular structures obtained from bats in different taxonomic groups: short-tailed leaf-nosed bats (Phyllostomidae, *Carollia*) and rousettes (Pteropodidae, *Rousettus*) [32].

Researchers from Saudi Arabia conducted a serological investigation in the territory of Oman to reveal MERS-CoV in the populations of farm animals. It showed that 100% of dromedaries (*Camelus dromedarius*) had antibodies against subunit S1 of the spike protein MERS-CoV. Further, direct evidence was obtained of the circulation of MERS-CoV variants identical to the epidemic ones in the organism of camels and the possibility of infection of humans from these animals [33]. Wing-handed animals contaminated camels during their day's rest in the barns for livestock. It was revealed that there were no specific antibodies in dromedaries to MERS-CoV in Africa, including Canary Islands [32]. Along with this, specific antibodies to MERS-CoV lacked in dromedaries in Australia [34], which indicated that these animals could not be the main host of MERS-CoV. Specific MERS antibodies were revealed in alpacas from Qatar (*Vicugna pacos*) [35]. Probably, all Tylopoda (Artiodactyla: Tylopoda) are sensitive to virus MERS-CoV and can be an intermediate link between the host and indicator of this virus if there is a natural reservoir –Chiroptera that contain the virus. This suggestion agrees with the lack of specific immunity in Bactrian camels (*Camelus bactrianus*) in non-endemic for MERS-CoV territories in Kazakhstan [36], Mongolia [37], and Northern China [38].

Even though the search for hosts of MERS-CoV among farm animals (bovine cattle, horses, goats, sheep) did not bring results, these studies significantly stimulated the study of coronaviruses in the populations

of mammals apart from Chiroptera.

There is evidence of transmission of MERS-CoV from humans to humans and the only source of infection is an infected human. However, the transmission of MERS-CoV from a human to a human occurs only after close contact with an infected person, for example, in medical institutions or when the secondary infection is added.

Presently, in Saudi Arabia, MERS-CoV is a serious threat to the human population because millions of religious people from 184 countries travel to Hadj or Umru, which can provoke new epidemics with a wider areal of spread. The last case of infection with MERS-CoV was registered in Saudi Arabia in February 2020 in a senior man with several chronic diseases.

Coronavirus infection SARS-CoV-2

At the end of 2019, a novel lethal virus appeared in the People's Republic of China (PRC). The virus caused pneumonia in Hankow, Hubei province, China. The quick spread of the virus started the epidemics in China, which was followed by a pandemic. In February 2020, the World Health Organization (WHO) called the infection "COVID-19" (COronaVIrus Disease 2019)[1].

On February 11, 2020, the International Committee on the Taxonomy of Viruses called the novel coronavirus SARS-CoV-2. The genetic sequence of SARS-CoV-2 was similar to the sequence SARS-CoV at least by 79%.

The analysis of the genetic basis of S-protein Spike, conducted by the specialists of the leading scientific centers in the USA, Australia, and Great Britain, showed that because of the occurred mutations in the receptor-binding domain of spike-like proteins, SARS-CoV-2 (unlike other coronaviruses) acquired a capability of binding to ACE2 receptor. It was suggested that for such an uptake, ACE2 also had to undergo certain genetic changes. This shows that the capability of SARS-CoV-2 to infect humans is the result of natural selection [39–41].

The first cases of the disease were associated with the sea product market in Hankow that sells poultry and meat of exotic animals (bats, snakes, pangolins). However, the specialists from the tropical botanical garden in China Academy of Sciences concluded that it was not the primary focus of the disease spread because the first cases of infection with novel coronavirus were registered in November 2019 and were not connected [42]. Besides, an epidemiological association was established between the trips of patients to PRC from neighboring countries. The largest number of infected people was revealed in the southern-eastern part of China (84% of the total cases in PRC) [43].

SARS-CoV-2 is a one-strand RNA-containing virus. It is Group II by the classification of pathogenicity. SARS-CoV-2 is included in the list of dangerous diseases.

The genetic assay of the virus that caused the disease showed similarity with coronaviruses spread among horseshoe bats. However, it is still not known if the bats were the initial source of infection. Nowadays, the main pathway of infection is human to human.

Scientists quickly established that SARS-CoV-2 was highly contagious and it could survive up to 2 hours in the environment and from several hours to 2 days on the surfaces [44]. The incubation period after infection is up to 14 days. All age groups are susceptible to the virus. Senior patients with comorbid diseases are more prone to a severe form. The main sources of infection are the diseased, symptomless carriers, and patients in the incubation period. Until now, the main pathways of infection were droplet and contact. The vertical pathway between the mother and newborn was suspected when a newborn was diagnosed with the novel coronavirus infection 30 hours after the birth in a hospital in Hankow. Besides, it is suggested that infection gets to the organism via the conjunctiva because conjunctival epithelium can be infected with aerosol or other biological liquids containing virus [45].

At the beginning of the epidemic spread, virus properties had a stable character with the clonal identity of the virus SARS-CoV-2. Mass-scale screening studies allowed the researchers to reveal the initial evolutionary changes in the virus in different parts of the world. All the viruses mutate with time and SARS-CoV-2 is not an exception.

The sequencing showed that coronaviruses changed slower than the majority of other RNA viruses because of an enzyme that fixes potentially fatal errors of copying. The typical SARS-CoV-2 virus accumulates only two single-letter mutations per month in its genome. This rate is twice as lower than in flu and ¼ lower than in HIV. This study was conducted at the Basel University, Switzerland[2].

The study of the University College of London showed that in two viruses SARS-CoV-2 collected from

[1] Kenneth McIntosh Coronavirus disease 2019 (COVID-19): Epidemiology, virology, and prevention https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-and-prevention

[2] Electronic resource https://www.nature.com/articles/d41586-020-02544-6

different parts of the world, only 10 RNA letters out of 29,903 differed from each other. This allows specialists to monitor evolutionary changes in the virus. Lots of mutations are not significant for the capability of the virus to spread or cause diseases among humans. However, several genetic changes are evolutionary beneficial for the virus and promote its spreading capacity. For example, line B.1.1.7 ("British strain") is a phylogenetic cluster that quickly spreads in the south-east of England. Before it was isolated at the beginning of September 2020, this line accumulated 17 specific mutations, which indicated a significant evolution, probably, in the chronically infected host. On December 28, 2020, this variant was detected in nearly 28% of cases of SARS-CoV-2 infection in England, and population-genetic models suggest that this line spreads 56% quicker than others. Line B.1.1.7 spread when SARS-CoV-2 was revealed all over the world and started to dominate in the existing population of the circulating variants. This indicates a natural selection of the virus with higher transmissibility at the population level. The measures taken by public healthcare services (protective masks, social distancing, and limit on social gathering) should remain effective but the fight with a more transmissive ("more contagious") variant will require stricter measures worldwide. Eight mutations in line B.1.1.7 involve spike glycoprotein (S-protein). It is suggested that these mutations can influence the binding of ACE2 and virus replication. Another coronavirus strain, also with a mutation in the receptor-binding domain, quickly spreads in South Africa. The influence of the mutation on antigenicity is still understudied[1].

Since SAR-CoV-2 already spread in all the continents and the number of infected people is still growing, the primary task of the systems of healthcare all over the world is specific measures of prevention. In December 2020, different medical institutions and pharmaceutical companies were working on more than 200 potential vaccines.

On August 11, 2020, in Russia, a vaccine "Gam-Covid-Vac (Sputnik V)" was invented at the Scientific and Research Center of Epidemiology and Microbiology named after Gamaleya.

Later, on October 13, 2020, Russia announced the registration of another vaccine "EpiVacCorona" developed by the State Scientific Center of Virology and Biotechnology "Vector" (Rospotrebnadzor).

Another perspective variant that entered the stage of clinical studies is the whole-virion vaccine (Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of Russian Academy of Sciences, Moscow).

According to the WHO, in 2021, clinical studies of 63 candidate vaccines are carried out all over the world. It is proved that people have a high susceptibility to coronavirus: all age groups are prone to this disease. Antigen diversity of viruses provides a high rate of reinfection.

The appearance of new representatives of the coronavirus family provides the rationale for their further study to choose promising preventive (anti-epidemic) measures, improve specific prevention, and develop vaccines.

The current generation witnessed a pandemic that is extraordinary for modern life. Presently, specialists all over the planet are working on effective measures against COVID-19. Quarantine measures and sanctions are introduced for their violation. Humankind has yet to evaluate and comprehend the scale of the social-economic damage and consequences of human losses. Time will show how society will change after the COVID-19 pandemic.

Finansing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Щелканов М.Ю., Попова А.Ю. Дедков В.Г., Акимкин В.Г., Малеев В.В. История изучения и современная классификация Коронавирусов (Nidovirales: Coronaviridae) // *Инфекция и иммунитет*. - 2020. - Т.10, №2. - С. 221-246. DOI: 10.15789/2220-7619-HOI-1412
2. Li X., Luk H.K.H., Lau S.K.P., Woo P.C.Y. Human Coronaviruses: General Features. // *Reference Module in Biomedical Sciences*. – 2019. - B978-0-12-801238-3.95704-0. DOI: 10.1016/B978-0-12-801238-3.95704-0.

REFERENCES

1. Shchelkanov M.Yu., Popova A.Yu., Dedkov V.G., Akimkin V.G., Maleyev V.V. History of investigation and current classification of coronaviruses (Nidovirales: Coronaviridae). *Russian Journal of Infection and Immunity*. 2020;10(2):221-246. (In Russ.) DOI: 10.15789/2220-7619-HOI-1412
2. Li X, Luk HKH, Lau SKP, Woo PCY. Human Coronaviruses: General Features. *Reference Module in Biomedical Sciences*. 2019:B978-0-12-801238-3.95704-0. DOI: 10.1016/B978-0-12-801238-3.95704-0.

[1] Electronic resource https://jamanetwork.com/journals/jama/fullarticle/2775006

3. Львов Д.К., Колобухина Л.В., Дерябин П.Г. Коронавирусная инфекция. Тяжелый острый респираторный синдром // *Инфекционные болезни: Новости. Мнения. Обучение*. - 2015. - №4 (13). – С. 35-42. eLIBRARY ID: 25197472
4. Львов Д. К., Альховский С.В., Колобухина Л.В., Бурцева Е.И. Этиология эпидемической вспышки COVID-19 в г. Ухань (провинция Хубэй, Китайская Народная Республика), ассоциированной с вирусом 2019-ncov (Nidovirales, Coronaviridae, Coronavirinae, Betacoronavirus, Подрод Sarbecovirus): уроки эпидемии SARS-COV // *Вопросы вирусологии*. - 2020.- №1. – С. 6-15. DOI: 10.36233/0507-4088-2020-65-1-6-15
5. Шамшева О.В. Новый коронавирус COVID-19 (SARS-COV-2) // *Детские инфекции*. - 2020. – Т.19, №1. - С. 5-6. eLIBRARY ID: 42706398
6. Tyrrell D.A., Bynoe M.L. Cultivation of a novel type of common-cold virus in organ cultures. // *Br Med J*. – 1965. – V.1. – P.1467-1470. DOI: 10.1136/bmj.1.5448.1467
7. Almeida J.D., Berry D.M., Cunningham C.H., Hamre D., Hofstad M.S., et al. Virology: Coronaviruses. // *Nature*. – 1968. – V.220. – P. 650. DOI: 10.1038/220650b0
8. Bradburne AF, Somerset BA. Coronative antibody tires in sera of healthy adults and experimentally infected volunteers. // *J Hyg (Lond)*. – 1972. – V.70(2). – P.235-44. DOI: 10.1017/s0022172400022294
9. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. // *Proc Soc Exp Biol Med*. – 1966. –V.121(1). – P. 190-3. DOI: 10.3181/00379727-121-30734.
10. Akerlund A, Greiff L, Andersson M, Bende M, Alkner U, Persson CG. Mucosal exudation of fibrinogen in coronavirus-induced common colds. // *Acta Otolaryngol*. – 1993. – V.113(5). – P. 642-8. DOI: 10.3109/00016489309135878
11. Linden M, Greiff L, Andersson M, Svensson C, Akerlund A, et al. Nasal cytokines in common cold and allergic rhinitis. // *Clin Exp Allergy*. – 1995. – V.25(2). – P.166-72. DOI: 10.1111/j.1365-2222.1995.tb01022.x
12. Щелканов М.Ю., Колобухина Л.В., Львов Д.К. Коронавирусы человека (Nidovirales, Coronaviridae): возросший уровень эпидемической опасности // *Лечащий врач*. - 2013. - № 10. - С.49-54. eLIBRARY ID: 22592720
13. Чучалин А.Г. Тяжелый острый респираторный синдром (ТОРС) // *Русский медицинский журнал*. - 2003. - Т.11. 22(194). - С. 1197-1204.
14. *Медицинская вирусология: учебное пособие*. Под ред. И.И. Генералова. - Витебск, ВГМУ, 2017.
15. Woo P.C., Lau S.K., Lam C.S., Lau C.C., Tsang A.K., et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. // *J Virol*. – 2012. – V.86(7). – P.3995-4008. DOI: 10.1128/JVI.06540-11
16. Balboni A., Battilani M., Prosperi S. The SARS-like coronaviruses: the role of bats and evolutionary relationships with SARS coronavirus. // *New Microbiol*. – 2012. – V.35(1). – P. 1-16. PMID: 22378548.
17. Андрейчик М.А., Копча В.С., Нычик Н.А. Тяжелый острый респираторный синдром // *Международный медицинский журнал*. - 2003. - №3, - С. 98-102.
18. Fouchier R.A., Hartwig N.G., Bestebroer T.M., Niemeyer B., de Jong J.C., et al. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc Natl Acad Sci U S A*. 2004;101(16):6212-6. DOI: 10.1073/pnas.0400762101.
19. Lednicky J.A., Waltzek T.B., McGeehan E., Loeb J.C., Hamilton S.B., Luetke M.C. Isolation and genetic characterization of human coronavirus NL63 in primary human renal proximal

3. L'vov D.K., Kolobuhina L.V., Deryabin P.G. Coronavirus infection. Severe acute respiratory syndrome. *Infekcionnye bolezni: Novosti. Mneniya. Obuchenie*. 2015;4(13:35-42) (In Russ.). eLIBRARY ID: 25197472
4. Lvov D.K., Alkhovsky S.V., Kolobukhina L.V., Burtseva E.I. Etiology of epidemic outbreaks COVID-19 in Wuhan, Hubei province, Chinese People Republic associated with 2019-nCoV (Nidovirales, Coronaviridae, Coronavirinae, Betacoronavirus, Subgenus Sarbecovirus): lessons of SARS-CoV outbreak. *Problems of Virology*. 2020;65(1):6-15. (In Russ.) DOI: 10.36233/0507-4088-2020-65-1-6-15
5. Shamsheva O.V. New coronavirus NCOV-19 (SARS-COV-2). *Detskie infekcii*. 2020;19(1):5-6 (In Russ.). eLIBRARY ID: 42706398
6. Tyrrell DA, Bynoe ML. Cultivation of a novel type of common-cold virus in organ cultures. *Br Med J*. 1965;1(5448):1467-70. DOI: 10.1136/bmj.1.5448.1467
7. Almeida J.D., Berry D.M., Cunningham C.H., Hamre D., Hofstad M.S., Mallucci L., McIntosh K., Tyrrell D.A.J. Virology: Coronaviruses. *Nature*. 1968;220(5168):650. DOI: 10.1038/220650b0
8. Bradburne AF, Somerset BA. Coronative antibody tires in sera of healthy adults and experimentally infected volunteers. *J Hyg (Lond)*. 1972;70(2):235-44. DOI: 10.1017/s0022172400022294
9. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. *Proc Soc Exp Biol Med*. 1966;121(1):190-3. DOI: 10.3181/00379727-121-30734.
10. Akerlund A, Greiff L, Andersson M, Bende M, Alkner U, Persson CG. Mucosal exudation of fibrinogen in coronavirus-induced common colds. *Acta Otolaryngol*. 1993;113(5):642-8. DOI: 10.3109/00016489309135878
11. Linden M, Greiff L, Andersson M, Svensson C, Akerlund A, et al. Nasal cytokines in common cold and allergic rhinitis. *Clin Exp Allergy*. 1995;25(2):166-72. DOI: 10.1111/j.1365-2222.1995.tb01022.x
12. Shchelkanov M.YU., Kolobuhina L.V., L'vov D.K. Human coronaviruses (Nidovirales, Coronaviridae): the increased level of the epidemic danger. *Lechashchij vrach*. 2013;10:49-54. (In Russ.). eLIBRARY ID: 22592720
13. Chuchalin A.G. Severe acute respiratory syndrome (SARS). *Russkij medicinskij zhurnal*. 2003;11(194);1197-1204. (In Russ.).
14. Generalov I.I. ed. *Medicinskaya virusologiya: uchebnoe posobie*. Vitebsk, VGMU, 2017. (In Russ.).
15. Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *J Virol*. 2012;86(7):3995-4008. DOI: 10.1128/JVI.06540-11
16. Balboni A, Battilani M, Prosperi S. The SARS-like coronaviruses: the role of bats and evolutionary relationships with SARS coronavirus. *New Microbiol*. 2012;35(1):1-16. PMID: 22378548.
17. Andrejchik M.A., Kopcha V.S., Nychik N.A. Severe acute respiratory syndrome. *Mezhdunarodnyj medicinskij zhurnal*. 2003;3:98-102. (In Russ.).
18. Fouchier RA, Hartwig NG, Bestebroer TM, Niemeyer B, de Jong JC, et al. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc Natl Acad Sci U S A*. 2004;101(16):6212-6. DOI: 10.1073/pnas.0400762101.
19. Lednicky JA, Waltzek TB, McGeehan E, Loeb JC, Hamilton SB, Luetke MC. Isolation and genetic characterization of human coronavirus NL63 in primary human renal proximal tubular epithelial cells obtained from a commercial supplier, and

tubular epithelial cells obtained from a commercial supplier, and confirmation of its replication in two different types of human primary kidney cells. // *Virol J.* – 2013. – V. 10. – P.213. DOI: 10.1186/1743-422X-10-213

20. Van der Hoek L., Pyrc K., Jebbink M.F., Vermeulen-Oost W., Berkhout R.J., et al. Identification of a new human coronavirus. // *Nat Med.* – 2004. – V. 10(4). – P. 368-73. DOI: 10.1038/nm1024
21. Woo P.C., Lau S.K., Chu C.M., Chan K.H., Tsoi H.W., et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. // *J Virol.* – 2005. – V. 79(2). – P. 884-95. DOI: 10.1128/JVI.79.2.884-895.2005
22. Lau S.K., Woo P.C., Yip C.C., Tse H., Tsoi H.W., et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. // *J Clin Microbiol.* – 2006. – V.44(6). – P.2063-71. DOI: 10.1128/JCM.02614-05
23. Sloots T.P., McErlean P., Speicher D.J., Arden K.E., Nissen M.D., Mackay I.M. Evidence of human coronavirus HKU1 and human bocavirus in Australian children. // *J Clin Virol.* – 2006. – V.35(1). – P.99-102. DOI: 10.1016/j.jcv.2005.09.008
24. Arden K.E., Nissen M.D., Sloots T.P., Mackay I.M. New human coronavirus, HCoV-NL63, associated with severe lower respiratory tract disease in Australia. // *J Med Virol.* – 2005. – V.75(3). – P.455-62. DOI: 10.1002/jmv.20288
25. Chiu S.S., Chan K.H., Chu K.W., Kwan S.W., Guan Y., et al. Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. // *Clin Infect Dis.* – 2005. – V.40(12). – P.1721-9. DOI: 10.1086/430301
26. Vabret A., Dina J., Gouarin S., Petitjean J., Corbet S., Freymuth F. Detection of the new human coronavirus HKU1: a report of 6 cases. // *Clin Infect Dis.* – 2006. – V. 42(5). – P.634-9. DOI: 10.1086/500136
27. Bastien N., Anderson K., Hart L., Van Caeseele P., Brandt K., et al. Human coronavirus NL63 infection in Canada. // *J Infect Dis.* – 2005. – V.191(4). – P.503-6. DOI: 10.1086/426869
28. Щелканов М.Ю., Ананьев В.Ю., Кузнецов В.В., Шуматов В.Б. Ближневосточный респираторный синдром: когда вспыхнет тлеющий очаг? // *Тихоокеанский медицинский журнал.* - 2015. - № 2. -С. 94–98. eLIBRARY ID: 24275106
29. Müller M.A., Raj V.S., Muth D., Meyer B., Kallies S., et al. Human coronavirus EMC does not require the SARS-coronavirus receptor and maintains broad replicative capability in mammalian cell lines. // *mBio.* – 2012. – V.3(6). – P. e00515-12. DOI: 10.1128/mBio.00515-12
30. De Benedictis P., Marciano S., Scaravelli D., Priori P., Zecchin B., et al. Alpha and lineage C betaCoV infections in Italian bats. // *Virus Genes.* – 2014. – V.48(2). – P.366-71. DOI: 10.1007/s11262-013-1008-x
31. Gortazar C., Segalés J. Middle East respiratory syndrome (MERS) coronavirus: a new challenge for veterinarians? // *Vet Pathol.* – 2013. – V.50(6). – P.954-5. DOI: 10.1177/0300985813506391
32. Azhar E.I., El-Kafrawy S.A., Farraj S.A., Hassan A.M., Al-Saeed M.S., et al. Evidence for camel-to-human transmission of MERS coronavirus. // *N Engl J Med.* – 2014. – V.370(26). – P.2499-505. DOI: 10.1056/NEJMoa1401505
33. Corman V.M., Jores J., Meyer B., Younan M., Liljander A., et al. Antibodies against MERS coronavirus in dromedary camels, Kenya, 1992-2013. // *Emerg Infect Dis.* – 2014. – V.20(8). – P.1319-22. DOI: 10.3201/eid2008.140596
34. Crameri G., Durr P.A., Barr J., Yu M., Graham K., et al. Absence of MERS-CoV antibodies in feral camels in Australia: Implications for the pathogen's origin and spread. // *One Health.* – 2015. – V.1. – P. 76-82. DOI: 10.1016/j.onehlt.2015.10.003

confirmation of its replication in two different types of human primary kidney cells. *Virol J.* 2013;10:213. DOI: 10.1186/1743-422X-10-213

20. van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, et al. Identification of a new human coronavirus. *Nat Med.* 2004;10(4):368-73. DOI: 10.1038/nm1024
21. Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol.* 2005;79(2):884-95. DOI: 10.1128/JVI.79.2.884-895.2005
22. Lau SK, Woo PC, Yip CC, Tse H, Tsoi HW, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. *J Clin Microbiol.* 2006;44(6):2063-71. DOI: 10.1128/JCM.02614-05
23. Sloots TP, McErlean P, Speicher DJ, Arden KE, Nissen MD, Mackay IM. Evidence of human coronavirus HKU1 and human bocavirus in Australian children. *J Clin Virol.* 2006;35(1):99-102. DOI: 10.1016/j.jcv.2005.09.008
24. Arden KE, Nissen MD, Sloots TP, Mackay IM. New human coronavirus, HCoV-NL63, associated with severe lower respiratory tract disease in Australia. *J Med Virol.* 2005;75(3):455-62. DOI: 10.1002/jmv.20288
25. Chiu SS, Chan KH, Chu KW, Kwan SW, Guan Y, et al. Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. *Clin Infect Dis.* 2005;40(12):1721-9. DOI: 10.1086/430301
26. Vabret A, Dina J, Gouarin S, Petitjean J, Corbet S, Freymuth F. Detection of the new human coronavirus HKU1: a report of 6 cases. *Clin Infect Dis.* 2006;42(5):634-9. DOI: 10.1086/500136
27. Bastien N, Anderson K, Hart L, Van Caeseele P, Brandt K, et al. Human coronavirus NL63 infection in Canada. *J Infect Dis.* 2005;191(4):503-6. DOI: 10.1086/426869
28. Shchelkanov M.YU., Anan'ev V.YU., Kuznecov V.V., SHumatov V.B. Middle East respiratory syndrome: when will the smouldering fire break out? *Tihookeanskij medicinskij zhurnal.* 2015;2:94-98 (In Russ.). eLIBRARY ID: 24275106
29. Müller MA, Raj VS, Muth D, Meyer B, Kallies S, et al. Human coronavirus EMC does not require the SARS-coronavirus receptor and maintains broad replicative capability in mammalian cell lines. *mBio.* 2012;3(6):e00515-12. DOI: 10.1128/mBio.00515-12
30. De Benedictis P, Marciano S, Scaravelli D, Priori P, Zecchin B, et al. Alpha and lineage C betaCoV infections in Italian bats. *Virus Genes.* 2014;48(2):366-71. DOI: 10.1007/s11262-013-1008-x
31. Gortazar C, Segalés J. Middle East respiratory syndrome (MERS) coronavirus: a new challenge for veterinarians? *Vet Pathol.* 2013;50(6):954-5. DOI: 10.1177/0300985813506391
32. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, et al. Evidence for camel-to-human transmission of MERS coronavirus. *N Engl J Med.* 2014;370(26):2499-505. DOI: 10.1056/NEJMoa1401505
33. Corman VM, Jores J, Meyer B, Younan M, Liljander A, et al. Antibodies against MERS coronavirus in dromedary camels, Kenya, 1992-2013. *Emerg Infect Dis.* 2014;20(8):1319-22. DOI: 10.3201/eid2008.140596
34. Crameri G, Durr PA, Barr J, Yu M, Graham K, et al. Absence of MERS-CoV antibodies in feral camels in Australia: Implications for the pathogen's origin and spread. *One Health.* 2015;1:76-82. DOI: 10.1016/j.onehlt.2015.10.003
35. Reusken CB, Schilp C, Raj VS, De Bruin E, Kohl RH, et al. MERS-CoV Infection of Alpaca in a Region Where MERS-CoV is Endemic. *Emerg Infect Dis.* 2016;22(6):1129-31. DOI: 10.3201/eid2206.152113
36. Miguel E, Perera RA, Baubekova A, Chevalier V, Faye B, et al. Absence of Middle East Respiratory Syndrome Coro-

35. Reusken C.B., Schilp C., Raj V.S., De Bruin E., Kohl R.H., et al. MERS-CoV Infection of Alpaca in a Region Where MERS-CoV is Endemic. // *Emerg Infect Dis.* – 2016. – V.22(6). – P. 1129-31. DOI: 10.3201/eid2206.152113
36. Miguel E., Perera R.A., Baubekova A., Chevalier V., Faye B., et al. Absence of Middle East Respiratory Syndrome Coronavirus in Camelids, Kazakhstan, 2015. // *Emerg Infect Dis.* – 2016. – V.22(3). – P.555-7. DOI: 10.3201/eid2203.151284
37. Chan S.M., Damdinjav B., Perera R.A., Chu D.K., Khishgee B., et al. Absence of MERS-Coronavirus in Bactrian Camels, Southern Mongolia, November 2014. // *Emerg Infect Dis.* – 2015. – V. 21(7). – P.1269-71. DOI: 10.3201/eid2107.150178
38. Liu R., Wen Z., Wang J., Ge J., Chen H., Bu Z. Absence of Middle East respiratory syndrome coronavirus in Bactrian camels in the West Inner Mongolia Autonomous Region of China: surveillance study results from July 2015. // *Emerg Microbes Infect.* – 2015. – V.4(12). – P.e73. DOI: 10.1038/emi.2015.73
39. Белоцерковская Ю.Г., Романовских А.Г., Смирнов И.П. COVID-19: респираторная инфекция, вызванная новым коронавирусом: новые данные об эпидемиологии, клиническом течении, ведении пациентов. // *Consilium Medicum.* – 2020. – Т. 22, №3. – С. 12–20. DOI: 10.26442/20751753.2020.3.200092
40. Xu X., Chen P., Wang J., Feng J., Zhou H., et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. // *Sci China Life Sci*. – 2020. – V.63(3). – P.457-460. DOI: 10.1007/s11427-020-1637-5
41. Jaimes J.A., Millet J.K., Stout A.E., André N.M., Whittaker G.R. A Tale of Two Viruses: The Distinct Spike Glycoproteins of Feline Coronaviruses. // *Viruses.* – 2020. – V.12(1). – P. 83. DOI: 10.3390/v12010083
42. Wang W., Tang J., Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. // *J Med Virol.* – 2020. – V.92(4). – P.441-447. DOI: 10.1002/jmv.25689
43. Малинникова Е.Ю. Новая коронавирусная инфекция. Сегодняшний взгляд на пандемию XXI века // *Инфекционные болезни: Новости. Мнения. Обучение*. - 2020. -№2 (33). – С. 18-32. DOI: 10.33029/2305-3496-2020-9-2-18-32
44. van Doremalen N., Bushmaker T., Morris D.H., Holbrook M.G., Gamble A., et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. // *N Engl J Med.* – 2020. – V.382(16). – P.1564-1567. DOI: 10.1056/NEJMc2004973
45. Lu C.W., Liu X.F., Jia Z.F. 2019-nCoV transmission through the ocular surface must not be ignored. // *Lancet*. – 2020. – V.395(10224). – P. e39. DOI: 10.1016/S0140-6736(20)30313-5

navirus in Camelids, Kazakhstan, 2015. *Emerg Infect Dis.* 2016;22(3):555-7. DOI: 10.3201/eid2203.151284
37. Chan SM, Damdinjav B, Perera RA, Chu DK, Khishgee B, et al. Absence of MERS-Coronavirus in Bactrian Camels, Southern Mongolia, November 2014. *Emerg Infect Dis.* 2015;21(7):1269-71. DOI: 10.3201/eid2107.150178
38. Liu R, Wen Z, Wang J, Ge J, Chen H, Bu Z. Absence of Middle East respiratory syndrome coronavirus in Bactrian camels in the West Inner Mongolia Autonomous Region of China: surveillance study results from July 2015. *Emerg Microbes Infect.* 2015;4(12):e73. DOI: 10.1038/emi.2015.73
39. Belotserkovskaia Yu.G., Romanovskikh A.G., Smirnov I.P. COVID-19: a respiratory infection caused by new coronavirus: new data on epidemiology, clinical course, and patients management. *Consilium Medicum.* 2020;22(3):12–20. (In Russ.). DOI: 10.26442/20751753.2020.3.200092
40. Xu X, Chen P, Wang J, Feng J, Zhou H, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci*. 2020;63(3):457-460. DOI: 10.1007/s11427-020-1637-5
41. Jaimes JA, Millet JK, Stout AE, André NM, Whittaker GR. A Tale of Two Viruses: The Distinct Spike Glycoproteins of Feline Coronaviruses. *Viruses*. 2020;12(1):83. DOI: 10.3390/v12010083
42. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J Med Virol.* 2020;92(4):441-447. DOI: 10.1002/jmv.25689
43. Malinnikova E.Yu. New coronaviral infection. Today's look at the pandemic of the XXI century. *Infektsionnye bolezni: novosti, mneniya, obuchenie [Infectious Diseases: News, Opinions, Training]*. 2020;9(2):18-32. (In Russ.). DOI: 10.33029/2305-3496-2020-9-2-18-32
44. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med.* 2020;382(16):1564-1567. DOI: 10.1056/NEJMc2004973
45. Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet.* 2020;395(10224):e39. DOI: 10.1016/S0140-6736(20)30313-5

Информация об авторах

Кононенко Анна Александровна, младший научный сотрудник лаборатории санитарной охраны территории, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID 0000-0002-7929-1095, email: anna270391@yandex.ru.

Носков Алексей Кимович, к.м.н. директор, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID 0000-0003-0550-2221, email: noskov-epid@mail.ru.

Водяницкая Светлана Юрьевна, к.м.н., главный специалист (инфекционист) отдела лечебной помощи взрослому населению управления лечебно-профилактической помощи Минздрава РО, Ростов-на-Дону, Россия. ORCID 0000-0002-2175-4261, email: s_vodyanitskaya@mail.ru.

Information about the authors

Anna A. Kononenko, Junior Researcher of the Laboratory of Sanitary Protection of the territory of the Rostov-on-Don Anti-Plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID 0000-0002-7929-1095, email: anna270391@yandex.ru.

Alexey K. Noskov, Cand. Sci. (Med), Director of the Rostov-on-Don Anti-Plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID 0000-0003-0550-2221, email: noskov-epid@mail.ru.

Svetlana Y. Vodyanitskaya, Can. Sci (Med), Chief specialist (infectious disease specialist) Department of Medical Care for Adults of the Department of Medical and Preventive Care Ministry of Health RO, Rostov-on-Don, Russia. ORCID 0000-0002-2175-4261, email: s_vodyanitskaya@mail.ru.

Подойницына Оксана Андреевна, к.б.н., научный сотрудник лаборатории микробиологии холеры; Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID 0000-0002-9996-4189, email: oksankashalu@yandex.ru.

Oksana A. Podoinitsyna, Cand. Sci (Bio), Researcher at the Laboratory of Cholera Microbiology; Rostov-on-Don Anti-Plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID 0000-0002-9996-4189, email: oksankashalu@yandex.ru.

Вклад авторов

Кононенко А.А. — написание текста рукописи;
Носков А.К. — обработка информации;
Водяницкая С.Ю. — обработка информации;
Подойницина О.А. — написание текста рукописи.

Authors contribution

Kononenko A.A. — writing the text of the manuscript;
Noskov A.K. — information processing;
Vodyanitskaya S.Yu. — information processing;
Podoynitsyna O.A. — the writing of the manuscript text.

Получено / Recived: 11.02.2021
Принято к печати / Accepted: 19.02.2021

УДК: 615.214.32
DOI 10.21886/2219-8075-2021-12-1-24-32

The new molecular targets for antidepressants

Yu.V. Kuznetsov, D.V. Evdokimov, I.I. Abramets

M. Gorkiy Donetsk National Medical University, Donetsk, DPR

The efficacy of depressive disorders treatment is insufficient. It is explained by an incomplete understanding of both pathogenesis of depression and antidepressants mechanism action. An improvement of the treatment efficacy of depression disorders is closely associated with complete knowledge of the pathogenesis of disorders and antidepressant mechanism of action. The effect produced by the first line of antidepressants prescribed currently in the clinical practice includes the accumulation of monoamines and prolonged activation of their membrane receptors. However, a decrease in the membrane receptors density evoked by prolonged activation of monoaminergic receptors is counteracted by the second line of antidepressant activity. It is associated with the expression of inducible regulatory protein S100A10 (p11) and its partners. In this review, the authors examined the structure and function of protein p11, its interaction with such proteins as annexin A2, Ahnak, chromatin-remodeling factor SMARCA3. The authors analyzed the influence of p11 on the membrane density of serotonin 5-HT1B and 5-HT4 receptors, metabotropic glutamate receptors 5, voltage-dependent potassium Kv3, and calcium Cav1.2 and 1.3 channels, that play an important role in both the effect of antidepressants and the pathogenesis of depression disorders. A systematic literature search was conducted in Scopus, Web of Science, MedLine, elibrary, and other databases.

Keywords: depression disorders, antidepressants, p11, membrane receptors, ionic channels..

For citation: Kuznetsov Yu.V., Evdokimov D.V., Abramets I.I. The new molecular targets for antidepressants. *Medical Herald of the South of Russia.* 2021;12(1):24-32. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-24-32.

Corresponding author: Yuriy V. Kuznetsov, far6@yandex.ru.

Новые молекулярные мишени действия антидепрессантов

Ю.В. Кузнецов, Д.В. Евдокимов, И.И. Абрамец

Донецкий национальный медицинский университет им. М. Горького, Донецк, ДНР

Эффективность лечения депрессивных расстройств недостаточна. Это обусловлено неполным пониманием как патогенеза депрессии, так и механизмов действия антидепрессантов. Повышение эффективности лечения депрессивных расстройств тесно связано с получением более полных представлений о патогенезе заболевания и механизмах действия антидепрессантов. Первая линия действия применяемых сейчас антидепрессантов — накопление моноаминов и длительная активация мембранных рецепторов. Однако снижению плотности мембранных рецепторов, обусловленному включением гомеостатических механизмов вследствие длительной активации рецепторов, противодействует вторая линия активности антидепрессантов. Она связана с экспрессией под действием антидепрессантов индуцибельного регуляторного белка S100A10 (p11) и его партнёров. В обзоре рассмотрены структура и функции белка p11, его взаимодействие с белками аннексином A2, Ahnak, регулятором хроматина SMARCA3. Проанализировано влияние p11 на мембранную плотность серотониновых 5-HT1B и 5-HT4 рецепторов, метаботропных глутаматных рецепторов 5, потенциалозависимых калиевых Kv3 и кальциевых Cav1.2 и 1.3 каналов, которые играют существенную роль как в действии антидепрессантов, так и в патогенезе депрессивных расстройств. Системный поиск литературы проводился по базам данных Scopus, WebofScience, MedLine, elibrary и другим.

Ключевые слова: депрессивные расстройства, антидепрессанты, p11, мембранные рецепторы, ионные каналы.

Для цитирования: Кузнецов Ю.В., Евдокимов Д.В., Абрамец И.И. Новые молекулярные мишени действия антидепрессантов. *Медицинский вестник Юга России.* 2021;12(1):24-32. DOI 10.21886/2219-8075-2021-12-1-24-32.

Контактное лицо: Юрий Васильевич Кузнецов, far6@yandex.ru.

Introduction

Major depressive disorder occurs with a lifetime probability of 20% to 25% in women, 7% to 12% in men. Despite seventy years of intensive research, the pathophysiology of this disorder is yet to be fully understood. Treatment of depression is complex since the effect comes with a great latency, is not universally observed, and the therapy has multiple adverse effects [1]. Apparently, treatment of depressive disorders must be made more effective, which requires a better understanding of its pathogenesis and antidepressant pharmacology.

There are different functional classes of antidepressants today: selective and non-selective inhibitors of serotonin, noradrenaline, and dopamine reuptake, as well as monoamine oxidase inhibitors; they amplify the signaling pathway of cAMP, increase the levels of Gas in neuron membranes, and activate adenylate cyclase-coupled monoamine receptors, which activates protein kinase A (PKA) in neuron cytoplasm and nuclei. PKA, calcium/calmodulin-dependent protein kinase type IV (CAMK4) and mitogen-activated protein kinases (MAPK) phosphorylate and activate CREB, a transcription factor that enables protein production. An increase in the activity of PKA, MAPK ERK1/2, and CREB on top of continuous administration of antidepressants results in higher levels of mRNA, neurotrophins, and growth factors. The latter enable normal neuron functional, synaptogenesis and neurogenesis in the dentate gyrus, as well as homeostatic processes in neural networks [2, 3].

Therefore, **the first line** affected by antidepressants consists of positively adenylate cyclase-coupled monoaminergic receptors, N-methyl-D-aspartate (NMDA) glutamate receptors, metabotropic glutamate receptors, M choline receptors, etc. Since chronic administration of monoaminergic antidepressants results in a long-term increase in the extracellular concentration of monoamines in the brain, membrane receptors respond naturally to disrupted homeostasis by reducing their density. However, such chronic treatment also produces interesting collisions: the change in the membrane density of the same receptors varies from region to region in the brain. For instance, the density and activity of 5-HT1A receptors decreases in the somato-dendritic synapses of raphe nuclei while increasing in the hippocampus and in the cortex, where the levels of 5-HT1B and 5-HT4 receptors rise as well. Membrane density of alpha2 adrenoreceptors decreases in the somato-dendritic synapses of the locus coeruleus while increasing in the neurons of forebrain structures, even though the density of beta adrenoreceptors decreases there [4].

The therapeutic effects of selective serotonin reuptake inhibitors (SSRIs), which are the most popular antidepressants today, come from activating 5-HT1B and 5-HT4 receptors. However, it remains unclear why the membrane density of these receptors increases rather than decreases whilst SSRIs persistently raise the levels of serotonin in the extracellular fluid. It has been discovered in the last decade that the phenomenon is a result of serotonin receptors interacting with the inducible regulatory protein p11 also known as S100A10, nerve growth factor-induced 42C, calpactin I light chain, annexin light chain [5].

p11, its functions and partners

The protein is a member of S100, a family of low-molecular-weight (11–12 kDa) acidic proteins. Its structure shown in Figure 1 has two EF hands binding Ca2+. A loop (a hinge) between the second and the third spiral enables the molecule to bend. The protein forms homodimers that can form heterotetramers with annexin A2, a cytoskeleton protein. Beside membrane receptors, p11 has been found to interact with Nav1.8, Kv, and H+ iron channels, with TRVP5 cation channels, as well as with the fragments: tissue plasminogen activator, phospholipase A2, etc. [5, 6].

Nevertheless, the role of p11 and its targets in the development of the depressive behavioral phenotype and in antidepressant effects remains unclear due to a multitude of contradictory facts. On the one hand, administering antidepressants, levodopa (an anti-Parkinson medication), and serotonin (5-HT) has been found to increase the levels of mRNA and p11 in the murine cortex and hippocampus, effects mediated by the signaling pathways of neurotrophins, receptor tyrosine kinase TrkB, and protein kinase ERK. On the other hand, pro-depressive glucocorticoids, interleukins, tumor necrosis factor, and interferons also increase the levels of p11 in the rodent cortex and hippocampus [7]. Besides, non-steroidal anti-inflammatory drugs (NSAIDs) have been found to inhibit the SSRI-induced increase in p11 and related behavioral effects whilst enhancing the same effects caused by other antidepressants [8]. It is assumed that the depressogenic effect-associated increase in p11 is likely a homeostatic brain reaction that counters the development of depressive disorders.

Total p11 knockout causes the brain and the body to lose this protein, which triggers the development of depressive behavioral phenotype as shown by a change in the results of a whole behavioral test battery; it is also associated with a reduced effect of antidepressants on

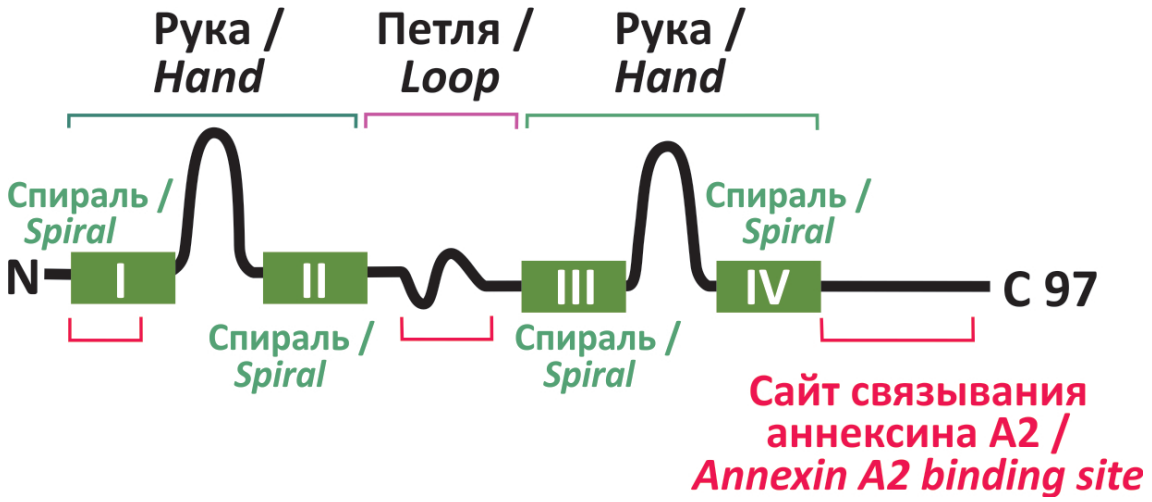

Figure 1. p11 structure. Roman numerals show spiralized molecule sites. The amino terminus to the left contains the site of binding to another p11 molecule, which is involved in forming a homodimer. The carboxyl terminus to the right contains the site of binding to annexin A2, which is involved in forming a heterotetramer.

Рисунок 1. Схематическое строение белка p11. Римскими цифрами отмечены спирализованные участки молекулы. Слева на амино-терминальном участке находится сайт связывания с другой молекулой p11 при образовании гомодимера. Справа карбокси-терминальный участок молекулы содержит сайт связывания аннексина A2 при образовании гетеротетрамера.

these indicators [9, 10]. Nucleus accumbens (NAcc) has been found to be the key structure involved in the development of depressive behavior in p11-deficient rodents. Indeed, suppressing p11 production in NAcc only by administering viral mRNAi reproduces all the signs of depressive behavior like total p11 knockout does. In intact mice, p11 levels in cholinergic NAcc interneurons are 30 times those in GABAergic medium spiny neurons; removal of p11 from cholinergic interneurons induces a depressive behavioral phenotype. On the contrary, excessive virus-associated p11 production in the same interneurons but not in dorsal striatum neurons eliminates behavioral disorders in total p11 knockout mice. Interestingly, p11 deficiency in cholinergic NAcc neurons does not diminish SSRI effects in mice when immobilized in tail suspension tests [11, 12]. Therefore, NAcc p11 is required to regulate emotions and mood, but not for antidepressants to have effect.

At the same time, p11 biosynthesis in cortical neurons is necessary for antidepressants to affect rodent behavior. For instance, chronic administration of antidepressants increases cortex and hippocampus p11 levels and boosts the expression of 5-HT4 receptors in p11-containing cortical murine neurons. Removing p11 from layer 5a projection neurons inhibits the behavioral effects of SSRIs and prevents the densifying of 5-HT4 receptors in neuron membranes whilst not affecting the signs of the depressive behavioral phenotype [9, 13].

How p11 Affects Serotonin and Glutamate Receptors of Membranes

Being a regulatory protein, p11 can by itself or in combination with other proteins interact with other target proteins and alter their activity. In the murine cortex, hippocampus, and NAcc, p11 is localized in close proximity to 5-HT1B/5-HT4 receptors in neuron membranes. p11 interacts with the third intracellular loop of serotonin receptors and increases their density in neuron membranes. This amplifies the cAMP-mediated signaling pathways of these receptors. However, p11 gene knockout suppresses the activity of 5-HT1B/4 receptors by reducing their density in neuron membranes [14, 15]. Therefore, p11 regulates membrane density rather than transcription and translation of serotonin receptors. In cultured cortical neurons, p11 enhances the effects of serotonin receptors on Ca2+ transmembrane current and protein kinase ERK1/2 activity. Serotonin and agonists of 5-HT1B receptors affect the phosphorylation of synapsin I, a presynaptic protein, and the corticostriatal glutamatergic synaptic transmission; these effects also depend on p11 [14].

Antidepressant-like effects of serotonin 1B and 4 receptor agonists in forced swim and tail suspension tests are weaker in p11 knockout mice compared to intact animals. The anxiolytic effects of these agonists are also reduced in p11-deficient mice subjected to open field tests [14]. 5-HT1B agonists have different effects on emotional learning in passive avoidance tests, disrupting

it in intact mice and boosting it in p11 knockout mice. Excessive p11 expression induced by viruses in dentate gyrus and in the CA1 region of the hippocampus caused emotional learning in p11 knockout mice to recover [16].

Studies of pyramidal corticostriatal neurons of the 5a layers of motor and sensory cortex in rats found that only some of these neurons expressed p11. These neurons have a higher electrical excitability compared to p11-negative pyramidal neurons; chronic administration of SSRIs increases the density of 5-HT2A rather than 5-HT4 receptors in the former. Stressogenic effects (chronic social isolation) reduced the density of 5-HT2A receptors in p11-positive pyramidal neurons whilst chronic administration of fluoxetine reversed this effect [15].

Aside from various serotonin receptors, p11 also interacts with cG protein-dependent metabotropic glutamate receptors (mGluRs). These receptors are divided into three groups: mGluR1 and mGluR5 in Group I, mGluR2 and mGluR3 in Group II, and mGluR4/6/7/8 in Group III. Behavioral studies found mGluR5 and mGluR2/3 blockers to have a rapidly developing antidepressant effect on mice. Besides, the mGluR5 cytoplasmic tail was found to have a p11 binding site consisting of a ser-thr-val amino acids sequence. Immunoprecipitation showed that p11/annexin A2 (Anxa2) heterotetramer was capable of binding to mGluR5. Testing on cultured HEK293 cell lines with embedded mGluR5 showed the effects of mGluR5 agonist to cause oscillations in the intracellular concentration of Ca2+, which would increase in case of excessive p11 production and decrease in case of damaged Anxa2. Therefore, p11/Anxa2 heterotetramers enhance the functioning of mGluR5. Further tests on the same cells, as well as on a COS-7 line, showed p11 and mGluR5 to co-increase their accumulation in cytoplasmic membranes, with p11 increasing the membrane density of mGluR5.

p11 and mGluR5 are found together in glutamatergic and GABAergic neurons. mGluR5 knockout in glutamatergic neurons prolonged the immobilization time in forced swim and tail suspension tests whilst reducing the sucrose preference, i.e., depressive behavioral phenotype progressed. The same procedure applied to GABAergic neurons caused an opposite change in behavior, i.e., it had an antidepressant-like effect. Similar results were obtained with p11 knocked out in GABAergic neurons. p11 knockout in glutamatergic neurons did not cause depressive behavior but made the mice more sensitive to chronic moderate stress. Another behavioral test (novelty-suppressed feeding) is used to characterize depressive and anxious behavior; this test found MPEP, an mGluR5 blocker, to have an antidepressant-like effect that would not manifest in p11 knockout mice. mGluR2/3 blocker also had an antidepressant-like effect, but that effect was not altered by removing p11. Therefore, the antidepressant-like effect of MPEP in intact mice could be eliminated by p11 knockout and reproduced by genetic deletion of mGluR5 in PV+ GABAergic interneurons [19]. The excitatory synaptic inputs of PV+ interneurons have effects that are known to stem from the activation of ionotropic AMPA and NMDA glutamate receptors, and mGluR5 increase the functional activity of NMDA receptors [20, 21]. Therefore, it can be assumed that the pharmacological or genetic suppression of mGluR5 activity inhibits the activity of PV+ GABAergic inhibitory interneurons and disinhibits glutamatergic pyramidal cortical and hippocampal neurons. Behavior-wise, this manifests itself as an antidepressant-like effect.

How p11 Affects Voltage-Gated Potassium and Calcium Channels

Beside serotonin and glutamate receptors, p11 also controls the membrane density and activity of potassium channels, which determines the excitability of neurons, as well as the duration and frequency of neural spike generation. In p11 knockout mice, the hippocampus was found to have suppressed transmembrane current through Kv3.1 potassium channels that are densely packed in the membranes of parvalbumin-positive (PV+) interneurons; this suppression was associated with a lower frequency of neuron discharge in response to depolarizing the membrane with a 100 pA step in inward current. HCN cation channel currents did not change under the same circumstances. Degradation and the resulting destruction of Kv3.1 channels caused a reduction of transmembrane currents in PV+ basket cells of the dentate gyrus. Besides, p11 knockout in dentate gyrus granule cells caused mice to have double the amplitude of GABAergic IPSPs due to optogenetic stimulation of PV+ interneurons. This was due to the loss of Kv3.1 channels in axon terminals of PV+ interneurons, which limit the duration of action potentials and the presynaptic release of GABA. p11 knockout in PV+ interneurons also caused more pronounced anxious behavior in a novel environment whilst compromising their resilience to depressogenic effects of protective social stress, even though sucrose preference and immobilization time in tail suspension tests did not change [22].

PV+ interneurons are important for cognition, emotions, learning, and memory. Emotional disorders, epilepsy, or schizophrenia can develop should these

neurons fail. In these neurons, Kv3 potassium channels accelerate spike repolarization and shorten the inter-spike interval; in presynaptic terminals of these neurons, Kv3 channels regulate GABA release and alter spike duration [23–25]. Interestingly, prefrontal and parietal cortical neurons have lower membrane density of Kv3.1 channels in schizophrenic patients; antipsychotics increase that density to health levels [26]. On the other hand, p11 knockout mice only had a lower density of Kv3.1 channels in hippocampus, but not in other brain structures, i.e. the mechanisms that control Kv3.1 density vary from structure to structure. Whilst chronic administration of antipsychotics increases the density of Kv3.1 channels in cortical structures, chronic administration of antidepressants reduces such density in the hippocampus. Chronically administered antidepressants have an inhibitory effect on Kv3.1 channels in PV+ dentate gyrus interneurons; this effect is associated with the activation of 5-HT5A receptors and PKA-induced phosphorylation of serine residue 503 in the Kv3.1b alpha subunit [27]. Therefore, it seems that the activity of Kv3.1 channels in PV+ interneurons is modulated by chronic administration of antidepressants, as it peaks early in treatment and is suppressed later on. Indeed, the initial effects of antidepressants cause the spike activity of PV+ interneurons to rise due to the activation of 5-HT1B receptors, a reduction in cAMP and in PKA activity, which reduces the phosphorylation of the Kv3.1 alpha subunit and boosts the functioning of Kv3.1 channels; however, the activity of these neurons attenuates further one due to down-regulation of Kv3.1 channels caused by the increased activity of 5-HT5A receptors [27].

Voltage-gated (VG) Ca2+ channels are another depression- and antidepressant-related molecular target of p11. Indeed, L type VG Ca29 channels enable the delivery of Ca2+ into neuron cytoplasm, activate CAMK4 and MAPK, and enhance the transcription processes. These channels are needed for neuron maturation, synaptic plasticity, and homeostasis of neural networks [28, 29]. Genetic research has shown that Cav1.2 (CACNA1C) polymorphism is associated with a higher risk of major depressive or bipolar disorders, or schizophrenia [29].

p11 interacts with serotonin receptors and potassium channels as a heterotetramer formed with Anxa2, a cytoskeleton protein. In turn, p11/Anxa2 can form a complex with the chromatin-remodeling factor SMARCA3. Knocking out the latter does not cause depressive behavioral phenotype to emerge and develop in mice; however, it mitigates the behavioral effects of SSRIs as well as their effects on neurogenesis [30]. p11/Anxa2 was later found to be able to form a complex with Ahnak, a high-molecular-weight (680 kDa) protein. This protein is involved in forming the gap junctions between epithelial cells in ventricular walls [30]. Ahnak was also found to be capable of binding to VG Ca2+ channel beta subunit in myocardiocytes and to be involved in regulating the density of Cav1.2 channels in the membranes of myocardiocytes, osteoblasts, and T cells [31, 32].

Biochemical studies on dentate gyrus and layers 2/3 of murine prefrontal cortex found Ahnak to stabilize the p11/Anxa2 complex; besides, the N-terminus of Ahnak interacts with the pore-forming L-type Ca channel alpha subunit, whilst the C-terminus interacts with the modulatory beta subunit of the same channel and with the p11/Anxa2 complex. Testing cultured embryo-derived cortical neurons revealed Ahnak knockout to reduce the total amplitude of Ca2+ currents by reducing the transmembrane current component associated with the activation of L-type calcium channels. Tests on the murine prefrontal cortex and hippocampus sections found layer 2/3 pyramidal neurons and PV+ interneurons of the dentate gyrus in Ahnak knockout mice to have reduced amplitude of calcium currents triggered by the activation of the Cav1.2 channels. Importantly, the total number of Cav1.2 and Cav1.3 alpha subunits and additional beta subunits would not change even in light of a 50% reduction in transmembrane currents. Consequently, triple protein complex p11/Anxa2/Ahnak regulates neuron membrane fixation of L-type calcium channels, but not the transcription or translation thereof [33].

Behavior-wise, Ahnak knockout mice had a depression-like phenotype manifesting as lower sucrose preference compared to water (a sign of anhedonia) and longer immobilization in swim and tail suspension tests. At the same time, local Ahnak knockout in glutamatergic neurons of the forebrain caused depression-like behavior in mice as indicated by a change in the behavioral test results. Local Ahnak knockout in PV+ interneurons had an antidepressant-like effect in sucrose preference and forced swim tests [33].

Interestingly, L-type Ca2+ channels regulate neuron excitability and spike generation. They employ several methods to this end: similarly to T-type Ca2+ channels (Cav3), L-type channel activation causes long-lasting depolarization of neuron membranes, which generates spikes; increased intracellular Ca2+ concentration activates BK channels, whilst depolarization excites VG Kv3.1 channels, and both types contribute to shortening the spikes while making them more frequent. This is why Ahnak knockout reduces the membrane density

of L-type channels in limbic glutamatergic neurons and suppresses their activity, causing a progressive depressive behavioral phenotype. On the other hand, local Ahnak knockout in PV+ interneurons suppresses their activity as well, but it also disinhibits cortical and hippocampal pyramidal neurons as is observed during the administration of fast-acting antidepressants: ketamine and mGluR5 blockers [34, 35].

Conclusions

In conclusion, it is safe to say the second line of antidepressant action comprises inducible regulatory proteins S100A10 (p11), annexin A2, etc., which can interact with membrane receptors and ion channels. Their intracellular carboxyl terminus or one of the intracellular loops contains a specific sequence of amino acids that determines the affinity to regulatory proteins. Besides, regulatory proteins can also interact with cytoskeleton elements. Complexes of these proteins regulate the transport of protein molecules and their fixation in membranes. Since chronic administration of antidepressants increases p11 levels in neurons, it causes a higher density of 5-HT1 and 5-HT4 receptors despite the homeostatic mechanism that has an opposite effect. On the other hand, serotoninergic and noradrenergic neurons of the afterbrain have low or no p11, causing a homeostatic response to antidepressants. That being said, complexes of p11, annexin A2, etc. stabilize and enhance the effects of monoaminergic and some fast-acting (e.g. mGluR5 blockers) antidepressants. Finally, total or local p11 knockout in the brain causes depressive disorders to progress, most likely due to disrupted fixation and change in the density of receptors and ion channels in neuron membranes.

Financing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Belmaker RH, Agam GN. Major depressive disorder. // *New Engl J Med*. – 2008. – V.358 (1). – P. 55–68. doi: 10.1056/NEJMra073096
2. Pittenger C, Duman RC. Stress, depression, and neuroplasticity: a convergence of mechanisms. // *Neuropsychopharmacology*. – 2008. – V.33 (1). – P. 88-109. doi: 10.1038/sj.npp.1301574
3. Tiraboschi E, Tardito D, Kasahara J, Moraschi S, Pruneri P, et al. Selective phosphorylation of nuclear CREB by fluoxetine is linked to activation of CaMK IV and MAP kinase cascades. // *Neuropsychopharmacology*. – 2004. – V. 29(10). – P.1831–1840. doi: 10.1038/sj.npp.1300488
4. Reuter LE, de Montigni C, Blier P. Electrophysiological characterization of the effect of long-term duloxetine administration on the rat serotonergic and noradrenergic systems. // *JPharmacolExpTher.* – 1998. – V.285 (2). – P. 404-412. PMID: 9580577
5. Svenningsson P, Greengard P. p11 (S100A10)-an inducible adaptor protein that modulates neuronal functions. // *Curr. Opin. Pharmacol.* – 2007. – V. 7 (1). – P.27–32. doi: 10.1016/j.coph.2006.10.001
6. Rescher U, Gerke V. S100A10/p11: family, friends and functions. // *Pflugers Arch.* – 2008. – V. 455(4). – P.575–582. doi: 10.1007/s00424-007-0313-4
7. Svenningsson P, Kim Y, Warner-Schmidt J, Oh Y-S, Greengard P. p11 and its role in depression and therapeutic responses to antidepressants. // *Nat Rev Neurosci.* – 2013. – V.14(10). – P.673–680. doi:10.1038/nrn3564
8. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective reuptake serotonine inhibitors (SSRIs) are attenuated by anti-inflammatory drugs in mice and humans. // *ProcNatlAcadSci U S A.* – 2011. – V.108(22). – P. 9262-9267. doi: 10.1073/pnas.1104836108
9. Warner-Schmidt JL, Chen EI, Zhang X, Marshal JJ, Morozov A, et al. A role for p11 in the antidepressant action of brain-

REFERENCES

1. Belmaker RH, Agam GN. Major depressive disorder. *New Engl J Med*. 2008;358(1):55–68. doi: 10.1056/NEJMra073096
2. Pittenger C, Duman RC. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*. 2008;33(1):88-109. doi: 10.1038/sj.npp.1301574
3. Tiraboschi E, Tardito D, Kasahara J, Moraschi S, Pruneri P, et al. Selective phosphorylation of nuclear CREB by fluoxetine is linked to activation of CaMK IV and MAP kinase cascades. *Neuropsychopharmacology*. 2004;29 (10): 1831–1840. doi: 10.1038/sj.npp.1300488
4. Reuter LE, de Montigni C, Blier P. Electrophysiological characterization of the effect of long-term duloxetine administration on the rat serotonergic and noradrenergic systems. *JPharmacolExpTher.* 1998;285(2):404-412. PMID: 9580577
5. Svenningsson P, Greengard P. p11 (S100A10)-an inducible adaptor protein that modulates neuronal functions. *Curr. Opin. Pharmacol.* 2007;7(1):27–32. doi: 10.1016/j.coph.2006.10.001
6. Rescher U, Gerke V. S100A10/p11: family, friends and functions. *Pflugers Arch.* 2008; 455 (4):575–582. doi: 10.1007/s00424-007-0313-4
7. Svenningsson P, Kim Y, Warner-Schmidt J, Oh Y-S, Greengard P. p11 and its role in depression and therapeutic responses to antidepressants. *Nat Rev Neurosci.* 2013; 14(10): 673–680. doi:10.1038/nrn3564
8. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective reuptake serotonine inhibitors (SSRIs) are attenuated by anti-inflammatory drugs in mice and humans. *ProcNatlAcadSci U S A.* 2011;108(22):9262-9267. doi: 10.1073/pnas.1104836108
9. Warner-Schmidt JL, Chen EI, Zhang X, Marshal JJ, Morozov A, et al. A role for p11 in the antidepressant action of brain-derived neurotrophic factor. *Biol. Psychiatry.* 2010; 68 (6):528–535. doi: 10.1016/j.biopsych.2010.04.029
10. Egeland M, Warner-Schmidt J, Greengard P, Svenningsson P. Neurogenic effects of fluoxetine are attenuated in

derived neurotrophic factor. // *Biol. Psychiatry.* – 2010. – V.68 (6). – P. 528–535. doi: 10.1016/j.biopsych.2010.04.029
10. Egeland M, Warner-Schmidt J, Greengard P, Svenningsson P. Neurogenic effects of fluoxetine are attenuated in p11 (S100A10) knockout mice. // *Biol. Psychiatry.* – 2010. – P.67 (11). – V. 1048–1056. doi: 10.1016/j.biopsych.2010.01.024
11. Warner-Schmidt JL, Schmidt EF, Marshall JJ, Rubin AJ, Arango-Lievano M, et al. Cholinergic interneurons in the nucleus accumbens regulate depression-like behavior. // *Proc. Natl Acad. Sci. USA*. – 2012. – V. 109 (28). – P. 11360–11365. doi: 10.1073/pnas.1209293109
12. Alexander B, Warner-Schmidt JL, Eriksson TM, Tamminga C, Arango-Lievano M, et al. Reversal of depressed behaviors in mice by p11 gene therapy in the nucleus accumbens. // *Science Transl Med.* – 2010. – V.2(54). – p.54ra76. doi: 10.1126/scitranslmed.3001079
13. Schmidt EF, Warner-Schmidt JL, Otopalik BG, Pickett SB, Greengard P, Heintz N. Identification of the cortical neurons that mediate antidepressant responses. // *Cell.* – 2012. – V.149 (5). – P. 1152–1163. doi: 10.1016/j.cell.2012.03.038
14. Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang XEl, et al. Alterations in 5-HT1B receptor function by p11 in depression-like states. // *Science.* – 2006. – P. 311 (5757). – P. 77–80. doi:10.1126/science.1117571
15. Warner-Schmidt JL, Flajolet M, Maller A, Chen EY, Qi H, et al. Role of p11 in cellular and behavioral effects of 5-HT4 receptorstimulation. // *J. Neurosci.* – 2009. – V. 29 (6). – P. 1937–1946. doi:10.1523/JNEUROSCI.5343-08.2009
16. Eriksson TM, Delagrange P, Spedding M, Popoli M, Mate AA, et al. Bidirectional regulation of emotional memory by 5-HT1B receptors involves hippocampal p11. // *Mol. Psychiatry.* – 2012. – V.17 (2). – P. 173-184. doi10.1038/mp.2010.131
17. Sargin D, Chottekalapanda RU, Perit KE, Yao V, Chu D, et al. Mapping the physiological and molecular markers of stress and SSRI antidepressant treatment in S100a10 corticostriatal neurons. // *Molecular Psychiatry*. – 2020. – V. 25 (6). – P. 1112–1129. doi: 10.1038/s41380-019-0473-6
18. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. // *Annu Rev PharmacolToxicol.* – 1997. – V.37. – P. 205–237. doi: 10.1146/annurev.pharmtox.37.1.205
19. Lee K-W, Westin L, Kim J, Chang JC, Oh Y-S, et al. Alteration by p11 of mGluR5 localization regulates depression-like behaviors. // *Mol Psychiatry.* – 2015. – V. 20(12). – P.1546–1556. doi:10.1038/mp.2015.132
20. Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. // *J Neurosci.* – 2000. – V. 20(21). – P.7871–7879. doi: 10.1523/JNEUROSCI.20-21-07871.2000
21. Rosenbrock H, Kramer G, Hobson S, Koros E, Grundl M, et al. Functional interaction of metabotropic glutamate receptor 5 and NMDA-receptor by a metabotropic glutamate receptor 5 positive allosteric modulator. // *Eur J Pharmacol.* – 2010. – V.639(1–3). – P. 40–46. doi: 10.1016/j.ejphar.2010.02.057
22. Seo SJ, Sveninngsson P. Modulation of ion channels and receptors by p11 (S100A10). // *Trends Pharmacol Sci.* – 2020. – V. 41 (7). – P. 487-497. doi: 10.1016/j.tips.2020.04.004
23. Rudy B, McBain CJ. Kv3 channels: voltage-gated K1 channels designed for high-frequency repetitive firing. // *Trends Neurosci.* – 2001. – V. 24. – P. 517–526. doi:10.1016/s0166-2236(00)01892-0
24. Hoppa MB, Gouzer G, Armbruster M, Ryan TA. Control andplasticity of the presynaptic action potential waveform at p11 (S100A10) knockout mice. *Biol. Psychiatry.* 2010; 67 (11):1048–1056. doi: 10.1016/j.biopsych.2010.01.024
11. Warner-Schmidt JL, Schmidt EF, Marshall JJ, Rubin AJ, Arango-Lievano M, et al. Cholinergic interneurons in the nucleus accumbens regulate depression-like behavior. *Proc. Natl Acad. Sci. USA*. 2012; 109 (28):11360–11365. doi: 10.1073/pnas.1209293109
12. Alexander B, Warner-Schmidt JL, Eriksson TM, Tamminga C, Arango-Lievano M, et al. Reversal of depressed behaviors in mice by p11 gene therapy in the nucleus accumbens. *Science Transl Med.* 2010; 2 (54):54ra76. doi: 10.1126/scitranslmed.3001079
13. Schmidt EF, Warner-Schmidt JL, Otopalik BG, Pickett SB, Greengard P, Heintz N. Identification of the cortical neurons that mediate antidepressant responses. *Cell.* 2012; 149 (5):1152–1163. doi: 10.1016/j.cell.2012.03.038
14. Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang XEl, et al. Alterations in 5-HT1B receptor function by p11 in depression-like states. *Science.* 2006; 311 (5757): 77–80. doi:10.1126/science.1117571
15. Warner-Schmidt JL, Flajolet M, Maller A, Chen EY, Qi H, et al. Role of p11 in cellular and behavioral effects of 5-HT4 receptorstimulation. *J. Neurosci.* 2009; 29 (6): 1937–1946. doi:10.1523/JNEUROSCI.5343-08.2009
16. Eriksson TM, Delagrange P, Spedding M, Popoli M, Mate AA, et al. Bidirectional regulation of emotional memory by 5-HT1B receptors involves hippocampal p11. *Mol. Psychiatry.* 2012; 17 (2): 173-184. doi10.1038/mp.2010.131
17. Sargin D, Chottekalapanda RU, Perit KE, Yao V, Chu D, et al. Mapping the physiological and molecular markers of stress and SSRI antidepressant treatment in S100a10 corticostriatal neurons. *Molecular Psychiatry*. 2020; 25 (6):1112–1129. doi: 10.1038/s41380-019-0473-6
18. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev PharmacolToxicol.* 1997; 37:205–237. doi: 10.1146/annurev.pharmtox.37.1.205
19. Lee K-W, Westin L, Kim J, Chang JC, Oh Y-S, et al. Alteration by p11 of mGluR5 localization regulates depression-like behaviors. *Mol Psychiatry.* 2015; 20(12): 1546–1556. doi:10.1038/mp.2015.132
20. Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. *J Neurosci.* 2000; 20(21):7871–7879. doi: 10.1523/JNEUROSCI.20-21-07871.2000
21. Rosenbrock H, Kramer G, Hobson S, Koros E, Grundl M, et al. Functional interaction of metabotropic glutamate receptor 5 and NMDA-receptor by a metabotropic glutamate receptor 5 positive allosteric modulator. *Eur J Pharmacol.* 2010; 639(1–3):40–46. doi: 10.1016/j.ejphar.2010.02.057
22. Seo SJ, Sveninngsson P. Modulation of ion channels and receptors by p11 (S100A10). *Trends Pharmacol Sci.* 2020; 41 (7): 487-497. doi: 10.1016/j.tips.2020.04.004
23. Rudy B, McBain CJ. Kv3 channels: voltage-gated K1 channels designed for high-frequency repetitive firing. *Trends Neurosci.* 2001; 24:517–526. doi:10.1016/s0166-2236(00)01892-0
24. Hoppa MB, Gouzer G, Armbruster M, Ryan TA. Control andplasticity of the presynaptic action potential waveform at small CNS nerve terminals. *Neuron.* 2014; 84 (4):778–789. doi: 10.1016/j.neuron.2014.09.038
25. Hu H, Roth FC, Vandael D, Jonas P. Complementary tuning of Na+ and K+ channel gating underlies fast and energy-efficient actionpotentials in GABAergic interneuron axons. *Neuron.* 2018;98(1):156–165.E6. doi: 10.1016/j.neuron.2018.02.024
26. Yanagi M, Joho RH, Southcott SA, Shukla AA, Ghose S, Tamminga CA. Kv3.1-containing K(1) channels are reduced in

small CNS nerve terminals. // *Neuron.* – 2014. – V.84(4). – P.778–789. doi: 10.1016/j.neuron.2014.09.038
25. Hu H, Roth FC, Vandael D, Jonas P. Complementary tuning of Na+ and K+ channel gating underlies fast and energy-efficient actionpotentials in GABAergic interneuron axons. // *Neuron.* – 2018. – V.98 (1). – P. 156–165.E6. doi: 10.1016/j.neuron.2018.02.024
26. Yanagi M, Joho RH, Southcott SA, Shukla AA, Ghose S, Tamminga CA. Kv3.1-containing K(1) channels are reduced in untreated schizophrenia and normalized with antipsychotic drugs. // *MolPsychiatry.* – 2014. – V.19(5). – P. 573–579. doi: 10.1038/mp.2013.49
27. Sagi Y, Medrihan L, George K, Barney M, McCabe KA, Greengard P. Emergence of 5-HT5A signaling in parvalbumin neurons mediates delayed antidepressant action. // *MolPsychiatry.* – 2020. – V.25 (6). – P. 1191–1201. doi: 10.1038/mp.2013.49
28. Simms BA, Zamponi GW. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. // *Neuron.* – 2014. – V. 82 (1). – P. 24–45. doi: 10.1016/j.neuron.2014.03.016
29. Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, et al. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. // *ProgNeurobiol.* – 2015. – V.134 (Nov). – P.36–54. doi: 10.1016/j.pneurobio.2015.09.002
30. Oh YS, Gao P, Lee KW, Ceglia I, Seo JS, et al. SMARCA3, a chromatin-remodeling factor, is required for p11-dependent antidepressant action. // *Cell.* – 2013. – V.152 (4). – P. 831–843. doi: 10.1016/j.cell.2013.01.014
31. Alvarez J, Hamplova J, Hohaus A, Morano I, Haase H, Vassort G. Calcium current in rat cardiomyocytes is modulated by the carboxylterminal ahnak domain. // *J Biol Chem.* – 2004. – V.279 (13). – P. 12456–12461. doi: 10.1074/jbc.M31217720
32. Matza D, Badou A, Kobayashi KS, Goldsmith-Pestana K, Masuda Y, et al. A scaffold protein, AHNAK1, is required for calcium signaling during T cell activation. // *Immunity.* – 2008. – V. 28 (1). – P. 64–74. doi: 10.1016/j.immuni.2007.11.020
33. Jin J, Bhatti DL, Lee K-W, Medrihan L, Jia Cheng J, et al. Ahnak scaffolds p11/Anxa2 complex and L-type voltage-gatedcalcium channel and modulates depressive behavior. // *Mol Psychiatry.* – 2020. – V. 25 (5). – P.1035–1049. doi:10.1038/s41380-019-0371-y
34. Striessnig J, Pinggera A, Kaur G, Bock G, Tuluc P. L-type Ca(2+) channels in heart and brain. // *Wiley Interdiscip Rev MembrTranspSignal.* – 2014. – V.3 (2). – P. 15–38. doi: 10.1002/wmts.102
35. Liu Y, Harding M, Pittman A, Dore J, Striessnig J, et al. Cav1.2 and Cav1.3 L-type calcium channels regulate dopaminergic firing activity in the mouse ventral tegmental area. // *J Neurophysiol.* – 2014. – V.112 (5). – P. 1119–1130. doi:10.1152/jn.00757.2013

untreated schizophrenia and normalized with antipsychotic drugs. *MolPsychiatry.* 2014; 19 (5):573–579. doi: 10.1038/mp.2013.49
27. Sagi Y, Medrihan L, George K, Barney M, McCabe KA, Greengard P. Emergence of 5-HT5A signaling in parvalbumin neurons mediates delayed antidepressant action. *MolPsychiatry.* 2020;25 (6):1191–1201. doi: 10.1038/mp.2013.49
28. Simms BA, Zamponi GW. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. *Neuron.* 2014;82 (1):24–45. doi: 10.1016/j.neuron.2014.03.016
29. Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, et al. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. *ProgNeurobiol.* 2015;134 (Nov):36–54. doi: 10.1016/j.pneurobio.2015.09.002
30. Oh YS, Gao P, Lee KW, Ceglia I, Seo JS, et al. SMARCA3, a chromatin-remodeling factor, is required for p11-dependent antidepressant action. *Cell.* 2013;152 (4):831–843. doi: 10.1016/j.cell.2013.01.014
31. Alvarez J, Hamplova J, Hohaus A, Morano I, Haase H, Vassort G. Calcium current in rat cardiomyocytes is modulated by the carboxylterminal ahnak domain. *J Biol Chem.* 2004;279 (13):12456–12461. doi: 10.1074/jbc.M31217720
32. Matza D, Badou A, Kobayashi KS, Goldsmith-Pestana K, Masuda Y, et al. A scaffold protein, AHNAK1, is required for calcium signaling during T cell activation. *Immunity.* 2008;28 (1):64–74. doi: 10.1016/j.immuni.2007.11.020
33. Jin J, Bhatti DL, Lee K-W, Medrihan L, Jia Cheng J, et al. Ahnak scaffolds p11/Anxa2 complex and L-type voltage-gatedcalcium channel and modulates depressive behavior. *Mol Psychiatry.* 2020; 25 (5):1035–1049. doi:10.1038/s41380-019-0371-y
34. Striessnig J, Pinggera A, Kaur G, Bock G, Tuluc P. L-type Ca(2+) channels in heart and brain. *Wiley Interdiscip Rev MembrTranspSignal.* 2014;3 (2):15–38. doi: 10.1002/wmts.102
35. Liu Y, Harding M, Pittman A, Dore J, Striessnig J, et al. Cav1.2 and Cav1.3 L-type calcium channels regulate dopaminergic firing activity in the mouse ventral tegmental area. *J Neurophysiol.* 2014;112 (5):1119–1130. doi:10.1152/jn.00757.2013

Информация об авторах

Кузнецов Юрий Васильевич, к.м.н., доц., доцент кафедры фармакологии и клинической фармакологии им. проф. И.В. Комиссарова, Донецкий национальный медицинский университет им. М. Горького, Донецк, ДНР. ORCID ID: 0000-0002-8368-5644.E-mail: far6@yandex.ru.

Евдокимов Дмитрий Владимирович, к.м.н., доц., доцент кафедры фармакологии и клинической фармакологии им. проф. И.В. Комиссарова, Донецкий национальный медицинский университет им. М. Горького, Донецк, ДНР. ORCID ID: 0000-0003-2989-7811. E-mail: evdokimov.dmitr@yandex.ru.

Information about the authors

Yuriy V. Kuznetsov, Cand. Sci. (Med), associate Professor of the I.V. Komissarov Department of Pharmacology and Clinical Pharmacology, M. Gorkiy Donetsk National Medical University, Donetsk, DPR. ORCID ID: 0000-0002-8368-5644.E-mail: far6@yandex.ru.

Dmitriy V. Evdokimov, Cand. Sci. (Med), associate Professor of the I.V. Komissarov Department of Pharmacology and Clinical Pharmacology, M. Gorkiy Donetsk National Medical University, Donetsk, DPR ORCID ID: 0000-0003-2989-7811.E-mail: evdokimov.dmitr@yandex.ru.

Абрамец Игорь Игоревич, д.м.н., проф., профессор кафедры фармакологии и клинической фармакологии им. проф. И.В. Комиссарова, Донецкий национальный медицинский университет им. М. Горького, Донецк, ДНР. ORCID ID: 0000-0002-2229-7541.E-mail: abramets4141@mail.ru.

Igor I. Abramets. Dr. Sci. (Med), full Professor of the I.V. Komissarov Department of Pharmacology and Clinical Pharmacology, M. Gorkiy Donetsk National Medical University, Donetsk, DPR. ORCID ID: 0000-0002-2229-7541.E-mail: abramets4141@mail.ru.

Вклад авторов

Ю.В. Кузнецов — обзор публикаций по теме статьи, написание текста рукописи;

Д.В. Евдокимов — обзор публикаций по теме статьи, написание текста рукописи;

И.И. Абрамец — обзор публикаций по теме статьи, написание текста рукописи..

Authors contribution

Y.V. Kuznetsov — review of publications on the topic of the article, writing the text of the manuscript;

D.V. Evdokimov — review of publications on the topic of the article, writing the text of the manuscript;

I.I. Abramets — review of publications on the topic of the article, writing the text of the manuscript.

Получено / Recived: 24.12.2020
Принято к печати / Accepted: 28.12.2020

УДК: 616.89-02-022
DOI 10.21886/2219-8075-2021-12-1-33-37

COVID-19 associated delirium: pathogenetic mechanisms of induction and clinical features

L.V. Tsoy

S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

The present review describes pathogenetic mechanisms and clinical features of COVID-19 associated delirium. Potential factors leading to the named condition and pathophysiological chains were described elaborately, including older adults' manifestation analysis based on the latest clinical studies. A systematic literature review was conducted in the following databases: PubMed, Scopus, e-library, Google Scholar and others.

Keywords: delirium, COVID-19, comorbidity, older adults.

For citation: Tsoy L.V. COVID-19 associated delirium: pathogenetic mechanisms of induction and clinical features. *Medical Herald of the South of Russia.* 2021;12(1):33-37. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-33-37.

Corresponding author: Lyudmila V. Tsoy, Lyudmila.tsoyy@gmail.com.

COVID-19-ассоциированный делирий: механизмы развития и особенности течения

Л.В. Цой

Казахский национальный медицинский университет им. С.Д. Асфендиярова, Алматы, Казахстан

Настоящий литературный обзор рассматривает механизмы развития COVID-19-ассоциированного делирия и особенности его клинических проявлений. Подробно описаны предрасполагающие к развитию данного состояния факторы и патофизиологические звенья, детали манифестации заболевания с симптомов делирия у пожилых лиц на основе анализа последних исследований. Системный поиск литературы производился по базам данных PubMed, Scopus, e-library, Google Scholar и др.

Ключевые слова: делирий, COVID-19, коморбидность, пожилой возраст.

Для цитирования: Цой Л.В. COVID-19-ассоциированный делирий: механизмы развития и особенности течения *Медицинский вестник Юга России.* 2021;12(1):33-37. DOI 10.21886/2219-8075-2021-12-1-33-37.

Контактное лицо: Людмила Владимировна Цой, lyudmila.tsoyy@gmail.com.

Introduction

First, the spread of coronavirus was reported in Hankow, the People's Republic of China, in December 2019 [1, 2]. The World Health Organization announced a pandemic of the novel coronavirus on March 11, 2020[1]. COVID-19 induces the development of severe acute respiratory syndrome (SARS) and is responsible for a high rate of morbidity and lethality worldwide [3]. Pandemic has turned global with the number of registered cases of more than 80 million and lethal cases – 1.8 million[2].

COVID-19 manifestations are diverse, varying from flu-like to gastrointestinal symptoms. Lately, more and more specialists have reported neuropsychiatric symptoms [4]. The studies show that in 20–30% of cases, patients with coronavirus infection develop delirium or changes in psychological status during hospitalization. In severe cases, such changes are registered in 60–70%

[1] Archived: WHO Timeline – COVID-19 https://www.who.int/news/item/27-04-2020-who-timeline-covid-19
[2] Johns Hopkins Coronavirus Resource Center https://coronavirus.jhu.edu/map.html

of patients regardless of the patient's age [5]. French scientists that analyzed the condition of patients from two intensive care units at the Hospital of the University of Strasburg reported that in 84% of patients with COVID-19-associated acute respiratory distress syndrome, neurological disturbances developed, in particular, delirium [6].

Delirium is an indicator of vital functions in serious senior patients. In senior patients, typical fibril response is often not established. Frequently, the disease manifestations do not include dyspnea even when hypoxia develops. In 40% of cases, infection with coronavirus cannot be verified by visual diagnostic methods, thus increasing the risk of underestimation of the patient's condition as a potential case of COVID-19 infection. For this reason, delirium should be considered as a part of screening criteria [7].

Since the present article contains the analysis of foreign studies, including American, the definition of the condition by DSM-5 should be provided. Delirium is a disturbance in attention and awareness that develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, tends to fluctuate in severity during a day, and is characterized by behavior impairments caused by somatic changes [8].

Mechanisms and potential factors of the development of COVID-19 delirium

Potential mechanisms of the development of COVID-19-associated delirium include hypoxemia, oxidative stress caused by respiratory distress syndrome, hypoperfusion, and uremia caused by polyorganic failure associated with respiratory distress syndrome [9, 10]. Another study also showed a multifactorial nature of delirium development including a direct effect on the central nervous system (CNS) by the virus and involvement of cerebral vessels in the pathological process. Indirect causes included hypoxia, high fever, dehydration, inflammatory reaction manifested as cytokine storm, and metabolic disorders [7]. Apart from the specified reasons, researchers believe that the indication of high doses of sedative myorelaxant drugs that simplify the patient's transfer to artificial pulmonary ventilation (APV), long-term APV, and social isolation play their roles in the development of delirium [11].

CNS damage caused by the novel coronavirus is explained by the fact that the virus is tropic to the cells that express the receptors to the angiotensin-converting enzyme-2 that are found in neural and glial cells, as well as the mucosal layer of the upper section of the esophagus, enterocytes, vascular endothelium, ciliated epithelium of the upper respiratory tract, and type 2 pneumocytes. The damage of these cells leads to the manifestation of respiratory syndromes [12, 13, 14]. The brain is sensitive to circulating components of the renin-angiotensin converting system (RAS). However, they do not exert a negative effect due to the impermeability of the hematoencephalic barrier (HEB). In case of infection with coronavirus, an inflammatory response develops in the organism, which increases the permeability of the HEB and leads to the massive infiltration of the brain with the components of the RAS. In turn, the components of the RAS induce neuroinflammatory cascade, which leads to vast neurodegeneration with further development of cognitive dysfunctions [15, 16].

The data obtained experimentally during the study of coronaviruses that existed before SARS-Cov2 demonstrated significant neurologic impairments in the structure of clinical manifestations, which is caused by the damage of the CNS, in particular, the hippocampus with the virus. The accumulation of the virus induces the inflammatory process in the brain with uncontrolled activation of astrocytes, which leads to astrogliosis and neutrophil infiltration that permeates the HEB due to its increased permeability caused by the inflammation. This leads to the damage of neurons of the brain, including the hippocampus, which leads to clinical manifestations of dementia and cognitive impairments. The inflammatory process in the CNS can be prolonged and lead to remote disturbances in its functioning. This can explain somatic-vegetative and psychic changes after COVID-19-associated delirium [17].

Some experimental data obtained from experiments that involved animals and people infected with *Coronaviridae* family viruses suggest the involvement of the brain stem and vasomotor center of the medulla in the pathological process [13, 18].

Clinical peculiarities of COVID-19-associated delirium

The study performed by Erica B. Baller *et al*. included 19 patients with COVID-19-associated delirium. The researchers observed patients with impaired consciousness, expressed agitation, and disturbed attention as the main manifestations of the disease in the case when there are no other respiratory symptoms and other signs of infection [4].

A group of American scientists from the Harvard School of Medicine described 4 clinical cases registered in the Massachusetts General Hospital. All the described patients were older than 65 years old and had

light cognitive impairments and moderate dementia in the anamnesis. It must be mentioned that all the patients did not have the main symptoms of COVID-19 (increased temperature, cough, dyspnea). The primary symptoms were the changes in the psychological status, which led to hospitalization. Only in 2 out of 4 patients, typical signs of coronavirus effect were revealed with visualizing methods of the examination (positive ground-glass opacities in the lower sections of the lungs). In one half of the observed patients, high temperatures were not registered. In the other half, the temperature was subfebrile. In all 4 cases, a significant level of C-reactive protein was observed, which could indicate an uncontrolled immune response that provoked delirium. Multifocal myoclonus was described in 3 patients. The authors believe that the development of myoclonus was expected because this symptom is a general manifestation of encephalopathy and signals global brain dysfunction. Still, they highlight that myoclonus in patients with COVID-19-associated delirium is more evident than delirium that is usually described in patients with other pathologies. Myoclonus was observed at admission in 2 patients that further developed increased muscular tonus with rigidity. This can be associated with the viral damage of the basal ganglia that are more sensitive to neurotropic viruses. Besides, it was reported that at a certain time during hospitalization, all patients stopped digesting food. In 3 of them, progressing anarthria was registered that started with a decrease in the language output and resulted in mutism, in some cases. The dynamic of the loss of speech was quick (several hours to several days) [9].

Italian scientists described the cases of delirium as a manifestation of coronavirus infection observed in the specialized department for patients with dementia at the Geriatric Institute named after Golgi in patients older than 65 years old. They established the dependence of the lethal outcomes on the character of the disease onset. At the initial stage of the development of the disease, 78.6% of lethal cases had the signs of delirium and not typical respiratory symptoms of COVID-19. In the majority of cases, lethality was associated with high comorbidity. Besides, the scientists highlight that the severity of dementia in patients included in the study did not correlate with the rate of lethality from COVID-19. In 52.2% of patients included in the study, a hypoactive variant of delirium was observed with decreased psychomotor functions. In 47.6% of patients, agitation and aggressive behavior were registered, which could be characterized as hyperactive delirium. In some cases, there was a shift from hyperactive to hypoactive delirium. Psychotic symptoms were described in 19% of patients with the developed delirium. American and Italian researchers agreed that delirium could be considered as the first symptom of coronavirus infection in senior people before the development of hypoxia, fever, and inflammatory response [19].

On the contrary, another British study showed the prevalence of the hyperactive variant of COVID-19-associated delirium (53% vs 37%) registered as hypoactive delirium [20].

More often, delirium symptoms appeared at the stage of SARS according to the data obtained by American scientists Jonathan P. Rogers *et al*. (consciousness impairment — 65% of patients hospitalized admitted to the intensive care unit, agitation — 69%, distorted consciousness — 21%) [21].

Andrea Ticinesi in his study revealed a correlation in the development of delirium between the age of patients and a high rate of lethality if delirium developed during the period of hospitalization [22].

There are data on a significant worsening of a physical condition manifested as post-resuscitation weakness, cognitive impairments, depression, and post-traumatic stress disorder after the resolution of delirium condition [17, 20].

Conclusion

COVID-19-associated delirium is the result of a combination of pathological factors in one patient, including senior age and comorbidity not only by somatic but also by psychic diseases, in particular, dementia and cognitive impairments.

Along with the typical manifestation of delirium according to DSM-5 classification (impairments of consciousness and attention), patients had myoclonus, muscular rigidity, and loss of speech output to mutism, which can take delirium as a global dysfunction o the brain.

At this stage, it is impossible to affirm that COVID-19-associated delirium is the primary manifestation of the disease in senior patients with high comorbidity. However, it is necessary to include diagnostic criteria of delirium in senior patients as potential manifestations of coronavirus infection for the monitoring of the development and prevention of complications.

Financing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Zhu N., Zhang D., Wang W., Li X., Yang B., et al. A novel coronavirus from patients with pneumonia in China, 2019. // N *Engl J Med*. - 2020. - V.382(8). - P.727–733. DOI: 10.1056/NEJMoa2001017
2. Green A. Li Wenliang. // *Lancet Infect Dis*. – 2020. – V395. – P.682. DOI: 10.1016/S0140-6736(20)30382-2
3. Peeri N.C., Shrestha N., Rahman M.S., Zaki R., Tan Z., et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? // *Int J Epidemiol.* – 2020. – V.49(3). – P. 717-726. DOI: 10.1093/ije/dyaa033
4. Baller E.B., Hogan C.S., Fusunyan M.A., Ivkovic A., Luccarelli J.W., et al. Neurocovid: Pharmacological Recommendations for Delirium Associated With COVID-19. // *Psychosomatics*. – 2020. – V. 61(6). – P.585-596. DOI: 10.1016/j.psym.2020.05.013
5. Mao L, Jin H, Wang M., Hu Y., Chen S., et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. // *JAMA Neurol.* - 2020. – V. 77(6). – P.683-690. DOI: 10.1001/jamaneurol.2020.1127
6. Helms J., Kremer S., Merdji H., Clere-Jehl R., Schenck M., et al. Neurologic features in severe SARS-CoV-2 infection. // *N Engl J Med*. – 2020. - V. 382(23). – P.2268-2270. DOI: 10.1056/NEJMc2008597
7. O'Hanlon S., Inouye S.K. Delirium: a missing piece in the COVID-19 pandemic puzzle. // *Age ageing*. – 2020. – V.49(4). – P.497-498. DOI: 10.1093/ageing/afaa094
8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5).* - American Psychiatric Publishing; 2013
9. Beach S.R., Praschan N.C., Hogan C., Dotson S., Merideth F., et al. Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement. // *Gen Hosp Psychiatry*. – 2020. – V.65. – P. 47–53. DOI: 10.1016/j.genhosppsych.2020.05.008
10. Yadav H, Kor D.J. Platelets in the pathogenesis of acute respiratory distress syndrome. // *Am J Physiol Lung Cell Mol Physiol*. – 2015. – V.309(9). - L915–23. DOI: 10.1152/ajplung.00266.2015
11. Kotfis K., Roberson S.W., Wilson J.E., Dabrowski W., Pun B.T., Ely E.W. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. // *Crit Care*. – 2020. - V.24. – P.176. DOI: 10.1186/s13054-020-02882-x
12. Baig A.M., Khaleeq A., Ali U., Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. // *ACS Chem Neurosci.* – 2020. – V.1(7). – P.995-998. DOI: 10.1021/acschemneuro.0c00122
13. Varga Z., Flammer A.J., Steiger P., Haberecker M., Andermatt R., et al. Endothelial cell infectionand endotheliitis in COVID-19. // *Lancet*. – 2020. – V.395(10234). – P.1417–1418. DOI: 10.1016/S0140-6736(20)30937-5.
14. Li Y.C., Bai W.Z., Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. // *J Med Virol*. - 2020. – V. 92(6). – P.552-555. DOI: 10.1002/jmv.25728
15. Palmer J.C., Tayler H.M., Love S. Endothelin-converting enzyme-1 activity, endothelin-1 production, and free radical-dependent vasoconstriction in Alzheimer's disease. // *J Alzheimers Dis*. – 2013. – V.36(3). – P.577–587. DOI: 10.3233/JAD-130383
16. Martire S., Mosca L., d'Erme M. PARP-1 involvement in neurodegeneration: a focus on Alzheimer's and Parkinson's diseases. // *Mech Ageing Dev*. – 2015. – V.146-148. – P.53–64. DOI: 10.1016/j.mad.2015.04.001

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. DOI: 10.1056/NEJMoa2001017
2. Green A. Li Wenliang. *Lancet Infect Dis*. 2020;395:682. DOI: 10.1016/S0140-6736(20)30382-2
3. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol*. 2020;49(3):717-726. DOI: 10.1093/ije/dyaa033
4. Baller EB, Hogan CS, Fusunyan MA, Ivkovic A, Luccarelli JW, et al. Neurocovid: Pharmacological Recommendations for Delirium Associated With COVID-19. *Psychosomatics*. 2020;61(6):585-596. DOI: 10.1016/j.psym.2020.05.013
5. Mao L, Jin H, Wang M, Hu Y, Chen S, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. DOI: 10.1001/jamaneurol.2020.1127
6. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270. DOI: 10.1056/NEJMc2008597
7. O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. *Age Ageing*. 2020;49(4):497-498. DOI: 10.1093/ageing/afaa094.
8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5).* - American Psychiatric Publishing; 2013
9. Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, et al. Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement. *Gen Hosp Psychiatry*. 2020;65:47-53. DOI: 10.1016/j.genhosppsych.2020.05.008
10. Yadav H, Kor DJ. Platelets in the pathogenesis of acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2015;309(9):L915-23. DOI: 10.1152/ajplung.00266.2015
11. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care*. 2020;24(1):176. DOI: 10.1186/s13054-020-02882-x
12. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998. DOI: 10.1021/acschemneuro.0c00122
13. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418. DOI: 10.1016/S0140-6736(20)30937-5.
14. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555. DOI: 10.1002/jmv.25728
15. Palmer JC, Tayler HM, Love S. Endothelin-converting enzyme-1 activity, endothelin-1 production, and free radical-dependent vasoconstriction in Alzheimer's disease. *J Alzheimers Dis*. 2013;36(3):577-87. DOI: 10.3233/JAD-130383
16. Martire S, Mosca L, d'Erme M. PARP-1 involvement in neurodegeneration: A focus on Alzheimer's and Parkinson's diseases. *Mech Ageing Dev*. 2015;146-148:53-64. DOI: 10.1016/j.mad.2015.04.001

17. Grist J.J., Marro B., Lane T.E. Neutrophils and viral-induced neurologic disease. // *ClinImmunol.* - 2018. – V.189. – P.52-56. doi: 10.1016/j.clim.2016.05.009
18. Li Y.C., Bai W.Z., Hirano N., Hayashida T., Hashikawa T. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. // *Virus Res.* – 2012. – V.163(2). – P.628–635. doi: 10.1016/j.virusres.2011.12.021
19. Yoshikawa N., Yoshikawa T., Hill T., Huang C., Watts D.M., et al. Differentialvirologicaland immunological outcome of severe acute respiratory syndrome coronavirus infection in susceptible and resistant transgenic mice expressing human angiotensin-converting enzyme 2. // *J Virol.* – 2009. – V.83(11). – P.5451-65. doi: 10.1128/JVI.02272-08.
20. Kotfis K., Roberson S.W., Wilson J., Pun B., Ely E.W., et al. COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? // *Anaesthesiol Intensive Ther.* - 2020. – V. 52(2). – P.132-138. doi: 10.5114/ait.2020.95164.
21. Garcez F.B., Aliberti M.J.R., Poco P.C.E., Hiratsuka M., Takahashi S., et al. Delirium and adverse outcomes in hospitalized patients with COVID-19. // *J Am Geriatr Soc.* – 2020. – V.68(11). - P.2440-46. doi: 10.1111/jgs.16803.
22. Alkeridy W.A., Almaghlouth I., Alrashed R., Alayed K., Binkhamis K., et al. A Unique Presentation of Delirium in a Patient with Otherwise Asymptomatic COVID-19. // *J Am Geriatr Soc.* – 2020. – V.68(7). – P.1382-1384.doi: 10.1111/jgs.16536
23. Poloni T.E., Carlos A.F., Cairati M., Cutaia C., Medici V., et al. Prevalence and prognostic value of Delirium as the initial presentation of COVID-19 in the elderly with dementia: An Italian retrospective study. // *EClinicalMedicine.* – 2020. – V.26. – P.100490. doi: 10.1016/j.eclinm.2020.100490
24. Mcloughlin B.C., Miles A., Webb T.E., Knopp P., Eyres C., et al. Functional and cognitive outcomes after COVID-19 delirium. // *EurGeriatr Med.* – 2020. – V.11(5). – P.857-862. doi: 10.1007/s41999-020-00353-8.
25. Rogers J.P., Chesney E., Oliver D., Pollak T.A., McGuire P., et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. // *Lancet Psychiatry.* – 2020. – V.7(7). – P.611-627. doi: 10.1016/S2215-0366(20)30203-0
26. Ticinesi A., Cerundolo N., Parise A., Nouvenne A., Prati B., et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. // *Aging ClinExp Res.* – 2020. – V.32(10). – P.2159-2166. doi: 10.1007/s40520-020-01699-6

17. Grist JJ, Marro B, Lane TE. Neutrophils and viral-induced neurologic disease. *ClinImmunol.* 2018;189:52-56. doi: 10.1016/j.clim.2016.05.009
18. Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. *Virus Res.* 2012;163(2):628-35. doi: 10.1016/j.virusres.2011.12.021
19. Yoshikawa N, Yoshikawa T, Hill T, Huang C, Watts DM, et al. Differential virological and immunological outcome of severe acute respiratory syndrome coronavirus infection in susceptible and resistant transgenic mice expressing human angiotensin-converting enzyme 2. *J Virol.* 2009;83(11):5451-65. doi: 10.1128/JVI.02272-08.
20. Kotfis K, Williams Roberson S, Wilson J, Pun B, Ely EW, et al. COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? *Anaesthesiol Intensive Ther.* 2020;52(2):132-138. doi: 10.5114/ait.2020.95164.
21. Garcez FB, Aliberti MJR, Poco PCE, Hiratsuka M, Takahashi SF, et al. Delirium and Adverse Outcomes in Hospitalized Patients with COVID-19. *J Am Geriatr Soc.* 2020;68(11):2440-2446. doi: 10.1111/jgs.16803.
22. Alkeridy WA, Almaghlouth I, Alrashed R, Alayed K, Binkhamis K, et al. A Unique Presentation of Delirium in a Patient with Otherwise Asymptomatic COVID-19. *J Am Geriatr Soc.* 2020;68(7):1382-1384. doi: 10.1111/jgs.16536.
23. Poloni TE, Carlos AF, Cairati M, Cutaia C, Medici V, et al. Prevalence and prognostic value of Delirium as the initial presentation of COVID-19 in the elderly with dementia: An Italian retrospective study. *EClinicalMedicine.* 2020;26:100490. doi: 10.1016/j.eclinm.2020.100490
24. Mcloughlin BC, Miles A, Webb TE, Knopp P, Eyres C, et al. Functional and cognitive outcomes after COVID-19 delirium. *EurGeriatr Med.* 2020;11(5):857-862. doi: 10.1007/s41999-020-00353-8.
25. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry.* 2020;7(7):611-627. doi: 10.1016/S2215-0366(20)30203-0
26. Ticinesi A, Cerundolo N, Parise A, Nouvenne A, Prati B, et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. *Aging ClinExp Res.* 2020;32(10):2159-2166. doi: 10.1007/s40520-020-01699-6

Информация об авторе

Цой Людмила Владимировна – обучающийся по программе резидентуры «Психиатрия», Казахский национальный медицинский университет им. С.Д. Асфендиярова, Алматы, Казахстан. ORCID 0000-0001-7134-2428. E-mail: lyudmila.tsoyy@gmail.com.

Information about the author

Lyudmila V. Tsoy – S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan. ORCID 0000-0001-7134-2428. E-mail: Lyudmila.tsoyy@gmail.com

Получено / Received: 26.12.2020
Принято к печати / Accepted: 13.01.2021

УДК: 616.711-002-08:616.89-008.454
DOI 10.21886/2219-8075-2021-12-1-38-45

Complex therapy for patients with ankylosing spondylitis with mixed anxiety–depressive disorder

I.I. Blaginina

St. Luke Luhansk State Medical University, Luhansk, LPR

Objective. The study aimed to evaluate the effect of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with melatonin on the dynamics of the quality of life (QOL), clinical and laboratory activity, and mixed anxiety–depressive disorder (MADD) in patients with ankylosing spondylitis (AS). **Materials and methods.** The study involved 65 patients with AS and RTDS. Patients from Group I (n=32) were prescribed melatonin at a dose of 3 mg per day at night, 30–40 minutes before bedtime, in addition to standard AS therapy. Patients from Group II (n = 33) received standard therapy. 8 weeks after, the dynamics of QOL indicators, clinical and laboratory activity, and the severity of MADD in patients from both groups were evaluated. **Results.** The application of melatonin in addition to standard therapy in patients with AS and MADD provided a statistically significant improvement in the functional and clinical-laboratory data (frequency and severity of anxiety and depression, pain syndrome indicators, ESR, CRP, integrative indicators of physical and psychological components of health). **Conclusion.** The application of melatonin in complex therapy for patients with AS and MADD contributes to the improvement of clinical and laboratory parameters, psychoemotional state, and QOL of this category of patients.

Keywords: ankylosing spondylitis, mixed anxiety–depressive disorder, quality of life, melatonin.

For citation: Blaginina I.I. Complex therapy for patients with ankylosing spondylitis with mixed anxiety–depressive disorder. *Medical Herald of the South of Russia.* 2021;12(1):38-45. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-38-45.

Corresponding author: Irina I. Blaginina, barry1803@yandex.ua.

Применение комплексной терапии в лечении больных анкилозирующим спондилитом с расстройствами тревожно-депрессивного спектра

И.И. Благинина

Луганский государственный медицинский университет им. Святителя Луки, Луганск, ЛНР

Цель: изучение влияния терапии нестероидными противовоспалительными препаратами (НПВП) в сочетании с мелатонином на динамику качества жизни (КЖ), клинико-лабораторную активность и расстройства тревожно-депрессивного спектра (РТДС) у пациентов с анкилозирующим спондилитом (АС). **Материалы и методы:** в исследовании приняли участие 65 пациентов с АС и РТДС. Пациентам I группы (n = 32) в дополнение к стандартной терапии АС назначался мелатонин в дозе 3 мг в сутки на ночь, за 30–40 минут до сна. Пациенты II группы (n = 33) получали стандартную терапию. Через 8 недель оценивали динамику показателей КЖ, клинико-лабораторной активности и выраженности РТДС больных обеих групп. Результаты: на фоне применения мелатонина в дополнение стандартной терапии пациентов с АС и РТДС отмечается статистически значимое улучшение функциональных и клинико-лабораторных данных (частота и уровень выраженности тревожности и депрессии, показателей болевого синдрома, СОЭ, СРБ, интегративных показателей физического и психологического компонентов здоровья). **Выводы:** применение мелатонина в комплексной терапии пациентов с АС и РТДС способствует улучшению клинико-лабораторных показателей, психоэмоционального состояния и КЖ данной категории больных.

Ключевые слова: анкилозирующий спондилит, расстройства тревожно-депрессивного спектра, качество жизни, мелатонин.

Для цитирования: Благинина И.И. Применение комплексной терапии в лечении больных анкилозирующим спондилитом с расстройствами тревожно-депрессивного спектра. *Медицинский вестник Юга России.* 2021;12(1):38-45. DOI 10.21886/2219-8075-2021-12-1-38-45.

Контактное лицо: Ирина Ивановна Благинина, barry1803@yandex.ua.

Introduction

The mutual effects of autoimmune inflammations and mental disorders are of interest for rheumatology today. To date, different rheumatological diseases are associated with a 7 to 15 times higher incidence of mixed anxiety-depressive disorders (MADDs) compared to the general population; this trend is reflected in many research papers, most of which deal with rheumatoid arthritis and systemic lupus erythematosus [1, 2].

Chronic pain syndrome associated with an immuno-inflammatory process has been found to be linked to a higher incidence of comorbidities that exacerbate the underlying disease, including MADDs. Constant pain alters the psycho-emotional status of patients, giving such manifestations as anxiety, depression, apathy, fatigue, excitability, and irritability [3, 4]. The conventional factors of risk of depression are: female sex, family history, social deprivation, lack of social support, chronic psychosocial stress, chronic pain, low work performance, negative thoughts about the disease found in autoimmune patients; these factors do contribute to MADDs.

There is no doubt to date that chronic inflammation is the primary pathophysiological mechanism for the development of psycho-emotional disorders including depression, the latter being considered a systemic disease associated with a higher level of inflammatory reaction markers: C-reactive protein (CRP), TNF-alpha, interleukin-1, and interleukin-6 [5, 6].

Mutual pathogenesis theory suggests that immuno-inflammatory diseases and MADDs have common triggers, in particular stress factors, and mostly similar pro-inflammatory pathogenesis, which means they can co-progress [7, 8]. Pro-inflammatory cytokines activate the hypothalamic-pituitary-adrenal axis (HPA axis) and, combined with the effects of stressors, stimulate another release of cytokines sensitizing the HPA axis, which worsens the vegetative support of the body and disrupts its adaptive capacities, thus exacerbating the endocrine dysfunction that regulates the stress and immune responses of the body; this increases the level of pro-inflammatory cytokines, giving such clinical manifestations as poor mood, chronic pain, fatigue, and sleep disturbances [9, 2].

Some research points to a high incidence and severity of MADDs in patients suffering seronegative spondyloarthritis, in particular psoriatic spondyloarthropathies and ankylosing spondylitis (AS) [10, 11]. Some studies cover the causes of psycho-emotional disorder development in AS males [12]. To date, however, drug-based treatment of AS+MADD patients remains an understudied topic.

Immune inflammation and MADDs have common pathogenic mechanisms in such patients; this means a modified approach is needed to treat AS coupled with MADD. Melatonin is commonly used to correct circadian rhythms; however, it has other proven clinical effects and seems a promising solution to the problem above. A broad range of melatonin effects (chronobiotic, antioxidant, cytoprotective, analgesic, and antiapoptotic effects) have been studied so far. However, it has less studied yet no less important peripheral anti-inflammatory effects associated with inhibiting COX-2 and NO synthase [13]. Clinical trials prove the medication to be an antidepressant as well [14, 15]. Noteworthy is the ability of melatonin to inhibit matrix metalloproteinase as found in patients with rheumatoid arthritis [16].

The **objective** hereof was to study how nonsteroidal anti-inflammatory drugs (NSAIDs) coupled with melatonin would affect the quality of life, clinical and laboratory test results, and MADDs in AS patients.

Materials and Methods

The study involved 65 AS patients, aged 25 to 58 (43.4±7.7), 41 males and 26 females, who on average had had the disease for 10.1 ± 4.6 years; 25 had university education. Thirty-four (52.3%) patients had disabilities: 21 (61.8%) with Cat. 3 disabilities, and 13 (38.2%) with Cat. 2 disabilities, mostly with Functional Class 3 disorders (69.2%). AS was diagnosed on the basis of modified New York criteria (ACR, 1984); the activity of the pathological process was estimated by the Bath AS disease activity index (BASDAI) according to the EULAR criteria. All the involved patients were registered to have the core diagnostic signs of mixed anxiety-depressive disorder (F41.2): depressed mood, loss of interest and pleasure, anxiety and unrest, as well as some additional symptoms: sleep disturbances and loss of appetite, impaired concentration, tension and fussiness, tremor, irritability, low libido. All the patients were offered psychiatric assistance since antidepressant treatment must be prescribed and monitored by a psychiatrist. However, most of the patients rejected partner treatment, i.e., co-treatment by the attending physician and a psychiatrist. For this reason, the researchers developed an alternative treatment relying on melatonin, as it has a clinically proven pleiotropic antidepressant effect [14; 15].

Inclusion criteria were: informed consent, verified AS diagnosis, AS lasting at least three years, and no diagnosed central nervous system disorders that might result in MADDs.

Pain syndrome, the duration of morning stiffness, and the patient's own health (POH) were evaluated by the patients themselves on the visual analog scale (VAS); laboratory readings were CRP and the erythrocyte sedimentation rate (ESR).

Spielberger's State-Trait Anxiety Inventory was used to assess the psycho-emotional state of the patients with scores below 30 being classified as mild anxiety, 30 to 45 as moderate anxiety, and >45 as severe anxiety. Hamilton Depression Scale (HDS) was used to detect signs of depression; the total score of 16 to 18 in young patients, 18 to 20 in elderly patients would indicate a non-psychotic depression. Taylor Manifest Anxiety Scale (TMAS) adapted for Russian patients by Nemchinov was used to assess anxiety. The questionnaire consisted of 50 yes/no questions. The score would depend on the patient's answers. The interpretation guideline was as follows: 0 to 5 points for mild anxiety; 5 to 15 for moderate-to-mild anxiety; 15 to 25 for moderate-to-severe anxiety; 20 to 40 for severe anxiety; 40 to 50 for very severe anxiety.

Quality of life (QoL) was tested using the Medical Outcomes Study Short Form (SF-36), a questionnaire that covers 8 concepts or scales of health: physical functioning, PF; role-physical functioning, RP; bodily pain, BP; general health, GH; vitality, VT; social functioning, SF; role-emotional, RE; and mental health, MH. SF-36 generally helps evaluate the physical status of health (PSH) and mental status of health (MSH). Each of the 8 scales is to be rated 0 to 100; the higher the score, the better the patient's status on the given scale [17].

Statistical testing of the results was done in Statistica 10.0 (Statsoft, USA). Normally distributed data is given herein as mean ± standard deviation (m±σ), else as Me (LQ-UQ), where Me is the median, LQ is the lower quartile, UQ is the upper quartile. To compare quantitative readings in groups before and after treatment, the authors used Wilcoxon's test; to compare two independent groups – Mann-Whitney's nonparametric U-test. Qualitative data was analyzed by means of contingency tables and χ^2. Differences were deemed significant at $p < 0.05$.

Results

Low activity was found in 17 patients, moderate activity in 32, and high activity in 16 at the beginning of this study. BASDAI averaged 3.9 (3.3; 4.3), being >4 in 40% of the patients and >7 in 4.6%. The Bath Ankylosing Spondylitis Functional Index (BASFI) was 4.1 (3.6; 4.6), being >4 in 52.3% of all cases and below 2 in 3.6%. ESR averaged 25.9 ± 8.7 mm/h, being normal in 17 (30.4%) patients. CRP averaged 19.7 ± 20.3 mg/l; being above 10 mg/l in 35 (53.8%) and above 50 mg/l in 7.7%.

Pain syndrome and morning stiffness in AS patients were as follows: 61.2±18.0 for spine pain, 61.6±17.6 mm for morning stiffness, 60.9±17.2 mm for POH. The severity of MADDs in the patients was as follows: HDS 17 for depression (14; 19), indicating non-psychotic depression in this age group; one Spielberger's scale, RA 32 (29; 37) and PA 40 (35; 44), 28 on Taylor's scale (19; 36), generally indicate moderately severe anxiety in the patients.

SF-36 QoL ratings were low both for the overall physical component score (PSH), which was 28.6 (26.6; 32.7), and for the overall mental component score (MSH), which was 39.2 (34.1; 42.9). PSH dropped seemingly due to a low RP of 25 (0; 25), reflecting the effects of the patient's physical status on their daily life, as well as the effects of their pain syndrome (BP) rated at 32 (22; 32). As for the mental component, they preserved relatively high SF values of 50 (37.5; 62.5) but had a low RE of 33.3 (33.3; 66.6) due to their emotional state.

Given the objectives hereof, all the patients were randomly sampled into two groups: Group 1 consisted of 32 patients who were treated throughout the study with an NSAID dosed equivalently to 150 mg of diclofenac (400 mg of celecoxib, 200 mg of nimesulide, 90 mg of etoricoxib, 200 mg of ketoprofen, or 200 mg of aceclofenac a day) plus 3 mg of melatonin 30 to 40 minutes before bedtime; Group II consisted of 33 patients treated the same way but without melatonin. As expected, the initial clinical and laboratory indicators of the patients did not differ significantly between the two groups ($p > 0.05$ in all cases).

Treatment was evaluated for effectiveness 8 weeks later using all the tested indicators (clinical and laboratory test results, anxiety, depression, and SF-36 scores). No adverse effects were reported throughout the study that would require canceling melatonin, such as morning drowsiness, fatigue, nightmares, or headaches.

All the examined patients had sleep disorders of varying nature and severity as of the start of the study. Shorter sleep was reported for 68.7% of the patients in Group I, 66.7% in Group II; nearly all the patients needed more time to fall asleep: 90.6% in Group I and 94% in Group II. Dissatisfaction with night sleep due to frequent awakenings was reported by 62.5%

of the patients in Group I, 66.7% in Group II; post-sleep fatigue in the morning was reported by 78.1% in Group I, 72.7% in Group II. The therapy made the sleep disorders milder and less frequent in Group I: only 21.8% still slept insufficiently long (χ^2 = 5.4; p = 0.02); 40.6% still reported that they needed more time to fall asleep (χ^2 = 3.8; p = 0.056); sleep dissatisfaction reporting fell to 28.1% (χ^2 = 2.9; p = 0.08), and morning fatigue only occurred in 31.3% (χ^2 = 4.2; p = 0.039). No positive trends were registered in Group II. Sleep dissatisfaction rates dropped only insignificantly (χ^2 = 0.6; p = 0.43), and so did post-sleep fatigue (χ^2 = 1.0; p = 0.32), both still reported by 48.5% in Group II.

At the end of the study, patients on melatonin had very significantly lower (p < 0.001) incidence and severity of depression per HDS, anxiety per TMAS, RA and PA. A significant reduction in PA and TMAS scores was found in Group II. Post-treatment comparison of the groups shows a significant (p < 0.05) reduction in anxiety in Group I. See Table 1 for the data.

Table 2 shows the laboratory indicators and pain syndrome data collected from both groups before and after treatment. These indicators had positive trends in both groups. Notably, Group I had a more significant reduction in BASDAI, BASFI, and spine stiffness than Group II. However, these differences were not significant. Post-treatment comparison in terms of POH, which had positive dynamics in both groups, revealed a significant difference (p = 0.025) in favor of Group I. This proves melatonin affects patients' emotions and personality. ESR and CRP improved significantly in both groups. Notably, Group I still had a greater improvement in both at p = 0.075 and p = 0.15, respectively.

The SF-36 questionnaire was used before and after treatment and showed that in Group I, physical health improved mainly in terms of the effects of physical condition and pain intensity on daily life as indicated by a 35.7% increase in PF, 22.6% increase in BP. Vitality, social and role functioning improved by 44%, 23%, and 49.6%, respectively, due to melatonin-associated mildening of depressive and psychovegetative disorders. These results are supported by the significant improvement in the integrative physical and mental components in Group I. In Group II, significant improvement was observed with respect to pain intensity and overall physical health. Post-treatment intergroup comparison showed significantly higher vitality mental component in melatonin-treated patients. See Table 3 for the data.

Discussion

Immuno-inflammatory diseases and MADDs have to date been proven to have similar pathogenic mechanisms based on response to stress that triggers

Table 1 / Таблица 1

Dynamics of indicators of anxiety and depression in groups
Динамика показателей тревоги и депрессии в группах

Параметр / *Parameter*	I группа (n = 32) / *I group*		II группа (n = 33) / *II group*		*Mann-Whitney U-test in groups after treatment*
	Исходно / *Baseline*	После лечения / *After treatment*	Исходно / *Baseline*	После лечения / *After treatment*	
ШДГ, баллы *HDS, points*	17 (16;20)	14 (12;16,5)	15 (13;17)	14 (13;17)	p=0,32
	p_1<0,001*		p_2=0,066		
TMAS, points	28 (19,5;36,5)	19,5(15,5;25,5)	27 (19;36)	25 (18;33)	p=0,014*
	p_1<0,001*		p_2<0,001*		
РТ, баллы *RA, points*	32,5 (29;36)	28,5 (27;32)	32 (28;38)	32 (28;39)	p=0,002*
	p_1<0,001*		p_2=0,88		
ЛТ, баллы *PA, points*	40 (34,5;44,5)	33 (30;36,5)	40 (36;41)	37 (35;43)	p=0,0008*
	p_1<0,001*		p_2=0,016*		

Note: ** — statistical significance of the differences (p ≤ 0.05); p_1 — significance of differences when comparing indicators before and after treatment of the I group; p_2 — significance of differences when comparing indicators before and after treatment of the II group.*
Примечание: * —показатели, при сравнении которых получены статистически значимые результаты (p ≤ 0,05); p1 — уровень статистической значимости различий при сравнении показателей до и после лечения I группы; p2 — уровень статистической значимости различий при сравнении показателей до и после лечения II группы.

Table 2 / Таблица 2

Dynamics of indicators of pain syndrome and clinical and laboratory activity in groups
Динамика показателей болевого синдрома и клинико-лабораторной активности в группах

Параметр / *Parameter*	I группа (n = 32) / *I group*		II группа (n = 33) / *II group*		*Mann-Whitney U-test in groups after treatment*
	Исходно / *Baseline*	После лечения / *After treatment*	Исходно / *Baseline*	После лечения / *After treatment*	
BASDAI, points	3,95 (3,4;4,5)	3,8 (3,3;4,17)	3,9 (3,3;4,25)	3,8 (3,2;4,15)	p=0,91
	p_1<0,001*		p_2=0,006*		
BASFI, points	4,18 (3,6;4,6)	3,9 (3,4;4,2)	4,1 (3,6;4,6)	3,9 (3,5;4,3)	p=0,75
	p_1<0,001*		p_2=0,002*		
Боль в позвоночнике, ВАШ *Spine pain, VAS*	64,5 (49;78)	54,5 (45;67)	58 (47;73)	50 (45;60)	p=0,2
	p_1=0,025*		p_2=0,001*		
Скованность, ВАШ *Stiffness, VAS*	64,5 (44;76,5)	49,5 (38;62,5)	65 (47;73)	55 (50;65)	p=0,086
	p_1=0,017*		p_2=0,04*		
СЗП, ВАШ *Patient's own health, VAS*	67,5 (42,5;78)	69 (60;77,5)	60 (50;72)	65 (55;72)	p=0,025*
	p_1=0,039*		p_2=0,039*		
СОЭ, мм/ч *ESR, mm/h*	26,5(18,5;30,5)	23 (19,5;25,5)	27 (21;31)	26 (20;28)	p=0,075
	p_1=0,018*		p_2=0,044*		
СРБ, мг/л *CRP, mg/l*	12 (7,8;24)	8,1 (6,4;11,2)	12 (8;15,6)	6,8 (5,3;12)	p=0,15
	p_1<0,001*		p_2<0,001*		

Note: ** — statistical significance of the differences ($p \le 0.05$); p_1 — significance of differences when comparing indicators before and after treatment of the I group; p_2 — significance of differences when comparing indicators before and after treatment of the II group.*
Примечание: * — знаком отмечены показатели, при сравнении которых получены статистически значимые результаты ($p \le 0,05$); p_1 — уровень статистической значимости различий при сравнении показателей до и после лечения I группы; p_2 — уровень статистической значимости различий при сравнении показателей до и после лечения II группы.

the HPA axis, resulting in increased catecholamine and cortisol levels, as well as in serotoninergic and noradrenergic deficiency [18]. Therefore, exposure to stress disrupts the homeostasis of neuroendocrine and immune systems, intensifying pain, activating negative perception of reality, and contributing to disadaptive behavior. Besides, constant pain and lack of adaptation to the disease, both being characteristic of AS+MADD patients, elevate the pain even further to close the 'vicious circle'.

Treatment of these patients should seek clinical and laboratory remission by inhibiting inflammation, mitigating pain, and improving the physical and mental QoL for better psycho-emotional stability.

Melatonin has a broad range of clinical effects listed herein whilst also having no severe side effects for up to 3 months of continuous administration; this allowed using it in addition to NSAIDs in AS+MADD patients that had clinical signs of anxiety-depressive disorders.

Findings suggest that this combined therapy not only improves the psycho-emotional status of patients but also stabilizes the QoL indicators and thus speeds up recovery from chronic pain and intense inflammation in AS+MADD patients.

Conclusions

Adding melatonin to the comprehensive treatment of AS in MADD-affected patients not only improves the emotional indicators such as incidence and intensity of sleep disturbances and anxiety-depressive disorders but also alleviates bodily pain, improves laboratory test results, and therefore enhances the quality of life of such patients.

Table 3 / Таблица 3

Dynamics of indicators of quality of life in groups
Динамика показателей качества жизни в группах

Параметр / *Parameter*	I группа (n = 32) / *I group*		II группа (n = 33) / *II group*		*Mann-Whitney U-test in groups after treatment*
	Исходно / *Baseline*	После лечения / *After treatment*	Исходно / *Baseline*	После лечения / *After treatment*	
PF, points	25 (20;35)	35 (35;62,5)	35 (25;40)	35 (25;40)	p=0,09
	p_1=0,003*		p_2=0,32		
RP, points	25 (0;25)	25 (25;50)	25 (0;25)	25 (0;50)	p=0,36
	p_1=0,009*		p_2=0,26		
BP, points	22 (22;41)	41 (27;41)	32 (22;32)	32 (22;41)	p=0,11
	p_1=0,004*		p_2=0,023*		
GH, points	43,5 (30;55)	55 (35;57,5)	35 (30;55)	40 (35;75)	p=0,49
	p_1=0,11		p_2=0,076		
VT, points	32,5 (10;42,5)	42,5 (35;45)	35 (30;45)	35 (35;45)	p=0,012*
	p_1<0,001*		p_2=0,38		
SF, points	50 (25; 56,25)	50 (50;62,5)	50 (50;62,5)	50 (50;62,5)	p=0,59
	p_1=0,004*		p_2=0,45		
RE, points	33,3 (0;66,6)	66,6(33,3;66,6)	33,3(33,3;66,6)	66,6(33,3;66,6)	p=0,14
	p_1=0,013*		p_2=0,57		
MH, points	44 (30;56)	52 (40;58)	40 (40;56)	40 (40;56)	p=0,47
	p_1=0,022*		p_2=0,1		
PSH, points	28 (25,9;33,5)	34,1(30,2;38,5)	29,2(27,6;32,5)	31 (30,2;35)	p=0,18
	p_1<0,001*		p_2=0,008*		
MSH, points	38,4 (33,8;43)	43,3(41,5;44,8)	40,6(35,1;41,8)	40,8 (38,9;43,2)	p=0,03*
	p_1<0,001*		p_2=0,12		

Note: ** — statistical significance of the differences ($p \le 0.05$); p_1 — significance of differences when comparing indicators before and after treatment of the I group; p_2 — significance of differences when comparing indicators before and after treatment o the II f group.*
Примечание: * — знаком отмечены показатели, при сравнении которых получены статистически значимые результаты ($p \le 0,05$); p_1 — уровень статистической значимости различий при сравнении показателей до и после лечения I группы; p_2 — уровень статистической значимости различий при сравнении показателей до и после лечения II группы.

Finansing. *The study did not have sponsorship.*
Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Margaretten M., Julian L., Katz P., Yelin E. Depression in patients with rheumatoid arthritis: description, causes and mechanisms // *Int. J. Clin. Rheumtol.* – 2011. – V.6(6). - P. 617-623. DOI: 10.2217/IJR. 11. 6
2. Лисицына Т.А., Вельтищев Д.Ю., Насонов Е.Л. Стрессовые факторы и депрессивные расстройства при рев-

REFERENCES

1. Margaretten M, Julian L, Katz P, Yelin E. Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *Int. J. Clin. Rheumtol.* 2011;6(6):617-23. DOI: 10.2217/IJR. 11. 6
2. Lisitsyna T.A., Veltischev D.Yu., Nasonov E.L. Stress factors and depressive disorders in rheumatic diseases. *Scientific and*

матических заболеваниях // *Научно-практическая ревматология*. – 2013. – Т. 51, № 2. – С. 98-103. DOI: 10.14412/1995-4484-2013-634
3. Барулин А.Е., Курушина О.В., Калинченко Б.М., Черноволенко Е.П. Хроническая боль и депрессия // *Лекарственный вестник*. – 2016. – Т. 10, № 1. – С. 3-10. eLIBRARY ID: 27316712
4. Miller A.H., Raison Ch.L. The role of inflammation in depression: from evolutionary imperative to modern treatment target // *Nature reviews. Immunology*. – 2016. - V.16. - P. 22-34. DOI: 10.1038/nri.2015.5
5. Howren M.B., Lamkin D.M., Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis // *Psychosom Med*. – 2009. – V.71. – P. 171-86. DOI: 10.1097/PSY.0b013e3181907c1b
6. Schmidt F.M., Lichtblau N., Minkwitz J.,Chittka T., Thormann J., et al. Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity // *J. Psychiatr. Res*. – 2014. - V.55. – P. 29-34. DOI: 10.1016/j.jpsychires. 2014.04.021
7. Лисицына Т.А., Вельтищев Д.Ю., Краснов В.Н., Насонов Е.Л. Клинико-патогенетические взаимосвязи иммуновоспалительных ревматических заболеваний и психических расстройств // *Клиническая медицина*. – 2014. – Т. 92, №1. – С. 12-20. eLIBRARY ID: 21179822
8. Abbott R., Whear R., Nikolaou V., Bethel A., Coon T., et al. Tumour necrosis factor-α inhibitor therapy in chronic physical illness: A systematic review and metaanalysis of the effect on depression and anxiety // *J. Psychosom Res*. – 2015. V.79 (3). – P. 175-184. DOI: 10.1016/j.jpsychores.2015.04.008
9. Rohleder N. Acute and chronic stress induced changes in sensitivity of peripheral inflammatory pathways to the signals of multiple stress systems // *Psychoneuroendocrinology*. – 2012. - V.37 (3). - P. 307-316. DOI: 10.1016/j.psyneuen.2011.12.015
10. Филимонова О.Г., Симонова О.В. Особенности качества жизни и вегетативного статуса у больных псориатическим артритом при тревожно-депрессивных расстройствах // *Фарматека*. – 2016. - №7. – С. 59–62. eLIBRARY ID: 26010197
11. Афанасьева Т.Ю., Гимадеева А.М., Афанасьева М.А., Сухорукова Е.В., Абдулганиева Д.И., Лапшина С.А. Оценка психологического состояния пациентов с анкилозирующим спондилитом и его влияния на качество лечения // *Вопросы организации и информатизации здравоохранения*. – 2016. – №S. – С. 36-38. eLIBRARY ID: 29855318
12. Peláez-Ballestas I., Boonen A., Vázquez-Mellado J., Reyes-Lagunes I., Hernández-Garduño A., et al. Coping Strategies for Health and Daily-Life Stressors in Patients With Rheumatoid Arthritis, Ankylosing Spondylitis, and Gout // *Medicine (Baltimore)*. – 2015. - V.94(10). – P. e600. DOI: 10.1097/MD.0000000000000600
13. Mayo J.C., Sainz R.M., Tan D.X., Hardeland R., Leon J., et al. Anti-Inflammatory Actions of Melatonin and Its Metabolites, N1-Acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-Acetyl-5-methoxykynuramine (AMK), in Macrophages // *Journal of Neuroimmunology*. – 2005. – V.165(1-2). – P. 139-149. DOI: 10.1016/j.jneuroim.2005.05.002
14. Den Boer J.A., Bosker F.J., Meesters Y. Clinical efficacy of agomelatine in depression: the evidence // *Int Clin Psychopharmacol*. - 2006. - V.21(1). – P. 21-24. DOI: 10.1097/01.yic.0000195661.37267.86
15. Loo H., Dalery J., Macher J.P., Payen A. Etude pilote comparant en aveugle l'effet thérapeutique de deux doses d'agomélatine - agoniste des récepteurs de la mélatonine et antagoniste des récepteurs 5HT2c - chez 30 patients [Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatoninergic agonist and selective 5HT2C

practical rheumatology. 2013;51(2):98-103. (In Russ.) DOI: 10.14412/1995-4484-2013-634
3. Barulin A.E., Kurushina O.V., Kalinchenko B.M., Chernovolenko E.P. Chronic pain and depression. *Medicinal Herald*. 2016;10(1):3-10. (In Russ.) eLIBRARY ID: 27316712
4. Miller AH, Raison ChL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature reviews. Immunology*. 2016;16:22-34. DOI: 10.1038/nri.2015.5
5. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-86. DOI: 10.1097/PSY.0b013e3181907c1b
6. Schmidt FM, Lichtblau N, Minkwitz J, Chittka T, Thormann J, et al. Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. *J Psychiatr Res*. 2014;55:29-34. DOI: 10.1016/j.jpsychires.2014.04.021
7. Lisitsyna T.A., Veltischev D.Yu., Krasnov V.N., Nasonov E.L. Clinical and pathogenetic relationships of immune-inflammatory rheumatic diseases and mental disorders. *Clinical Medicine*. 2014;92(1):12-20. (In Russ.) eLIBRARY ID: 21179822
8. Abbott R, Whear R, Nikolaou V, Bethel A, Coon JT, et al. Tumour necrosis factor-α inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety. *J Psychosom Res*. 2015;79(3):175-84. DOI: 10.1016/j.jpsychores.2015.04.008
9. Rohleder N. Acute and chronic stress induced changes in sensitivity of peripheral inflammatory pathways to the signals of multiple stress systems --2011 Curt Richter Award Winner. *Psychoneuroendocrinology*. 2012;37(3):307-16. DOI: 10.1016/j.psyneuen.2011.12.015
10. Filimonova O.G., Simonova O.V. Features of the quality of life and vegetative status in patients with psoriatic arthritis with anxiety-depressive disorders. *Pharmateca*. 2016;7:59–62. (In Russ.) eLIBRARY ID: 26010197
11. Afanasyeva T.Yu., Gimadeeva A.M., Afanasyeva M.A., Sukhorukova E.V., Abdulganieva D.I., Lapshina S.A. Assessment of the psychological state of patients with ankylosing spondylitis and its impact on the quality of treatment. *Issues of organization and informatization of healthcare*. 2016;S:36-38. (In Russ.) eLIBRARY ID: 29855318
12. Peláez-Ballestas I, Boonen A, Vázquez-Mellado J, Reyes-Lagunes I, Hernández-Garduño A, et al. Coping strategies for health and daily-life stressors in patients with rheumatoid arthritis, ankylosing spondylitis, and gout: STROBE-compliant article. *Medicine (Baltimore)*. 2015;94(10):e600. DOI: 10.1097/MD.0000000000000600
13. Mayo JC, Sainz RM, Tan DX, Hardeland R, Leon J, et al. Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages. *J Neuroimmunol*. 2005;165(1-2):139-49. DOI: 10.1016/j.jneuroim.2005.05.002
14. den Boer JA, Bosker FJ, Meesters Y. Clinical efficacy of agomelatine in depression: the evidence. *Int Clin Psychopharmacol*. 2006;21 Suppl 1:S21-4. DOI: 10.1097/01.yic.0000195661.37267.86
15. Lôo H, Daléry J, Macher JP, Payen A. Etude pilote comparant en aveugle l'effet thérapeutique de deux doses d'agomélatine - agoniste des récepteurs de la mélatonine et antagoniste des récepteurs 5HT2c - chez 30 patients [Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatoninergic agonist and selective 5HT2C receptors antagonist, in the treatment of major depressive disorders]. *Encephale*. 2002;28(4):356-62. (In French). PMID: 12232545.

receptors antagonist, in the treatment of major depressive disorders]. // *Encephale.* – 2002. – V.28(4). – P. 356–362. (In French). PMID: 12232545.
16. Rudra D.S., Pal U., Maiti N.C., Reiter R.J., Swarnakar S. Melatonin inhibits matrix metalloproteinase-9 activity by binding to its active site // *Journal of Pineal Research*. - 2013. - V.54(4). – P. 398-405. DOI: 10.1111/jpi.12034
17. Law L., Rehnman J.B., Deminger A., Klingberg E., Jacobsson E.T.H., Forsblad-d'Eliva H. Factors related to health-related quality of life in ankylosing spondylitis, overall and stratified by sex // *Arth. Res. Ther*. - 2018. – V.20(1). – P. 284. DOI: 10.1186/s13075-018-1784-8
18. Муслимова Е.В. Стратегии преодоления хронической боли при ревматоидном артрите // *Практическая медицина*. - 2014.- № 4(80). - С.72-74. eLIBRARY ID: 21845038

16. Rudra DS, Pal U, Maiti NC, Reiter RJ, Swarnakar S. Melatonin inhibits matrix metalloproteinase-9 activity by binding to its active site. *J Pineal Res*. 2013;54(4):398-405. DOI: 10.1111/jpi.12034
17. Law L, Beckman Rehnman J, Deminger A, Klingberg E, Jacobsson LTH, Forsblad-d'Elia H. Factors related to health-related quality of life in ankylosing spondylitis, overall and stratified by sex. *Arthritis Res Ther*. 2018;20(1):284. DOI: 10.1186/s13075-018-1784-8
18. Muslimova E.V. Strategies for overcoming chronic pain in rheumatoid arthritis. *Practical Medicine.* 2014;4(80):72-74. (In Russ.) eLIBRARY ID: 21845038

Информация об авторе

Благинина Ирина Ивановна, к.м.н., доцент, доцент кафедры внутренней медицины Факультета Последипломного Образования, Луганский государственный медицинский университет имени Святителя Луки», Луганск, ЛНР. ORCID: 0000-0002-9220-5841. E-mail: barry1803@yandex.ua.

Information about the author

Irina I. Blaginina, Cand. Sci. (Med.), associate professor; associate professor, Department of internal medicine, Faculty of Postgraduate Education, St. Luke Luhansk State Medical University, Luhansk, LPR. ORCID: 0000-0002-9220-5841. E-mail: barry1803@yandex.ua.

Получено / Received: 08.01.2021
Принято к печати / Accepted: 19.02.2021

УДК: 618.2/3:618.293
DOI 10.21886/2219-8075-2021-12-1-46-53

Daily periodicity of labor in pregnant women in physiological and complicated pregnancy depending on the sex of the fetus

T.L. Botasheva, V.O. Andreeva, E.Yu. Lebedenko, A.D. Fabricant, A.V. Khloponina, E.V. Zheleznyakova, O.P. Zavodnov

Rostov State Medical University, Rostov-on-Don, Russia

Objective: the study aimed to reveal the daily periodicity of labor, the nature of melatonin metabolism, and the outcome of childbirth in women with a physiological and complicated pregnancy, depending on the sex of the fetus. **Materials and methods:** to study the chronophysiological characteristics of birth outcomes depending on fetal sex, 1 980 birth histories and stories of newborns were analyzed. The neonates were born between January 1 and December 31, 2016, in a maternity ward of the Federal State Budgetary Educational Institution of Higher Education "RostGMU" of the Ministry of Health of Russia. Melatonin production was identified by the level of urinary excretion of 6-sulfatoxymelatonin (6-SM) (its main metabolite) examining the morning portion of the urine of women by the ELISA method (at 8 am 3 ml of urine were collected in Eppendorf tube). **Results:** it was revealed that fetal sex modulated the activity of the central regulatory mechanisms responsible for the daily period functional processes in the female body and the initiation of labor. The largest number of spontaneous births by male fetuses occurred in the early evening before midnight when daily illumination was decreased, while the birth of girls was observed more often in the period from midnight to early morning. At the same time, mothers of boys had lower production of melatonin compared to that of girls' mothers. **Conclusions.** The peculiarities of labor and birth complications associated with the sex of the fetus were identified.

Keywords: physiological pregnancy, placental insufficiency, daily biorhythms, time of the end of labor, melatonin metabolism, fetal sex.

For citation: Botasheva T.L., Andreeva V.O., Lebedenko E.Yu., Fabricant A.D., Khloponina A.V., Zheleznyakova E.V., Zavodnov O.P. Daily periodicity of labor in pregnant women in physiological and complicated pregnancy depending on the sex of the fetus. *Medical Herald of the South of Russia.* 2021;12(1):46-53. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-46-53.

Corresponding author: Tatyana L. Botasheva, t_botasheva@mail.ru.

Суточная периодичность родов при физиологической и осложнённой беременности в зависимости от пола плода

Т.Л. Боташева, В.О. Андреева, Е.Ю. Лебеденко, А.Д. Фабрикант, А.В. Хлопонина, Е.В. Железнякова, О.П. Заводнов

Ростовский государственный медицинский университет, Ростов-на-Дону, Россия

Цель: исследование характера суточной периодичности времени окончания родов, уровня мелатонина и исхода родов у женщин при физиологической и осложнённой беременности в зависимости от пола вынашиваемого плода. **Материалы и методы:** для изучения суточных биоритмов времени окончания родов в зависимости от половой принадлежности плода проанализированы 1980 историй родов и историй новорождённых. Уровень мелатонина определяли по содержанию в утренней порции мочи 6-сульфатоксимелатонина (6-СОМТ). **Результаты:** обнаружено, что пол плода определяет специфику плодо-материнских отношений, модулирующих функцию хронофизиологических регуляторных механизмов: для мужского пола плода наиболее характерно окончание самопроизвольных родов с раннего вечера до полуночи в условиях снижения суточной освещенности и более низком содержании 6-сульфатоксимелатонина в моче, тогда как для женского пола плода — с полуночи до раннего утра при более высокой продукции мелатонина. **Выводы:** установлены особенности характера родовой деятельности и осложнений в родах, связанные с полом плода.

Ключевые слова: пол плода, физиологическая беременность, плацентарная недостаточность, суточные биоритмы, время окончания родов, мелатониновый обмен.

Для цитирования: Боташева Т.Л., Андреева В.О., Лебеденко Е.Ю., Фабрикант А.Д., Хлопонина А.В., Железнякова Е.В., Заводнов О.П. Суточная периодичность родов у беременных при физиологической и осложненной беременности в зависимости от пола плода. *Медицинский вестник Юга России.* 2021;12(1):46-53. DOI 10.21886/2219-8075-2021-12-1-46-53.

Контактное лицо: Боташева Татьяна Леонидовна, t_botasheva@mail.ru.

Introduction

In the study of the obstetrical pathology mechanisms, a detailed study of integration mechanisms in the "mother – placenta – fetus" functional system (MPFFS) has great importance. Center and peripheral interactions in the MPFFS play a significant role in placental dysfunction pathogenesis [1–6].

According to the scant literature [7–11], one of the significant factors modulating the nature of fetal-maternal relationships in the MPFFS is the fetus gender. The evaluation category of these interactions is associated with a clear understanding that between the mother and the fetus organisms, mutual biochemical and hormonal signaling is carried out throughout the entire gestational period through the uteroplacental complex, which is a communication channel, and this signaling determines the formation of not just the MPFFS but also the "mother – placenta – female fetus" functional system" and "mother – placenta – male fetus functional system" with the characteristic options for the homeostatic balance of each of them [8].

The available data on the sexual dimorphism influence on the formation of obstetric pathology indicate that in 2014, the International Federation of Gynecology and Obstetrics recognized the male fetal gender (MFG) as a risk factor for the threat of premature birth [9, 11]. Data are presented that certain forms of chromosomal aberrations are associated with sexual dimorphism which is manifested in the biochemical and sonographic marker features [12–14]. It has been established that gestational diabetes mellitus (GDM) is more often recorded in cases of male childbearing [15, 16]. MFG is recognized as a risk factor for placental dysfunction [15, 17] and the female fetal gender (FFG) is accompanied by an increased risk of toxicosis and moderate preeclampsia, while its severe forms are most typical for MFG [8].

Biorhythms with varying frequency have particular importance in gestational tolerance formation: almost all functional processes in the MPFFS are cyclical. The greatest importance belongs to the "sleep-wake" circadian rhythm [18–20].

The circadian periodicity of labor, which is most dependent on the day/night cycle, is of the greatest interest from the gestational process standpoint. Thus, there is evidence of the existence of a clear relationship between the act of delivery duration and the day length: within different seasons, rapid labor occurs with greater frequency as the daylight increases [21, 22, 8].

In connection with the above, it is of considerable interest to study the relationship of the fetus gender during pregnancy and labor, taking into account the chronophysiological characteristics of the birth act.

The goal of the research was to study the nature of the daily frequency of labor, the characteristics of melatonin metabolism, and labor outcomes in women with physiological and complicated pregnancies, depending on the sex of the fetus.

Material and methods

The studies were carried out based on the FSBEI of Higher Education Rostov State Medical University of the Ministry of Health of the Russian Federation.

Before conducting the research, informed consent was obtained from each woman ("Rules for conducting high-quality clinical trials in the Russian Federation" dated December 29, 1998). There is an Ethics Committee Protocol of the Research Institute of Obstetrics and Pediatrics of Rostov State Medical University containing information on the approval of these studies (Protocol No. 23/2 dated April 25, 2013).

A total of 1101 women were examined: 584 primigravidas with physiological gestation and childbirth (Group I). Two hundred eighty of them had a female fetus (Group Ia) and 304 pregnant women had a male fetus (Group Ib). Group II included 517 primigravidas with placental dysfunction: 253 of them had a female fetus (group IIa), 264 – a male fetus (Group IIb). In Groups I and II, all patients had vaginal births without labor induction and stimulation.

Entry criteria in clinical Group I were uncomplicated singleton full-term pregnancy; 18 to 28 years old range; absence of obstetric pathology based on the results of clinical, hormonal, chemical, ultrasound, and Doppler studies. Exclusion criteria from Group I were pregnancies resulting from assisted reproductive technology programs; chromosomal aberrations and fetus congenital malformations; congenital malformations of organs and systems in women; extragenital and endocrine pathology; women refused to participate in the study. Criteria for inclusion in Group II were singleton full-term pregnancy; 18 to 28 years old range; Doppler signs of blood circulatory disturbances in the uteroplacental complex arteries; the asymmetric form of fetal growth retardation; deviations in the indicators of the fetus biophysical profile [23, 24].

The groups were randomized by the method of random numbers and "Flipping coin" [25].

Melatonin was determined based on the 6-sulfatoxymelatonin (6-SOMT) level in the morning urine.

The study of the outcome of labor was carried out based on the analysis of 1980 birth histories and the histories of newborns born from January 1 to December 31, 2016, at the maternity department of the FSBEI of Higher Education of the Rostov State Medical University of the Ministry of Health of Russia. The neonatal functional status was assessed using the Apgar scale.

Statistical data processing included the use of descriptive statistics (medians and Q1 and Q3). Statistical significance was calculated based on a 95% confidence level and a 0.05 accuracy of calculating statistical data.

Intergroup differences were determined using the nonparametric Kruskal-Wallis test; statistically significant differences were the basis for a posteriori analysis using the Mann-Whitney test. The initial data were processed using the IBM SPSS 26.0.0.1 and Excel 2016 programs. The circadian periodicity of the end of labor was carried out by Fourier time series analysis.

Results

An age distribution analysis of pregnant women in the examined sample revealed the predominance of 23–27-year-old women (60.9%), which is probably due to socio-economic transformations. An intragroup comparative analysis showed a similar prevalence of patients aged 23–27 years. In Group I, those were more by 25.4%, and in Group II – by 17.4% than younger pregnant women (p = 0.271).

The average age of menarche in the studied patients from Groups I and II was comparable and amounted to 11.7 ± 1.5 and 12.2 ± 1.3 years, respectively (p = 0.402).

Anamnestic data indicated that in both clinical groups, in most cases the menstrual cycle duration was 27–30 days (in Group I – 29 ± 1.2 and Group II – 28 ± 1.1 days) (p = 0.612).

Abnormal uterine bleeding characterized by an increase in the menstruation frequency (more than 38 days) was recorded in 7.0% of all women studied (42.1 ± 2.5 days in Group I and 38.3 ± 1.9 patients in Group II).

In most of the examined patients (75.0%, p = 0.021), the menstrual cycle duration was less than 8 days (in pregnant women in Group I – 4.7 ± 1.4, in Group II – 4.1 ± 2.1 days). There were no significant differences in the menstruation regularity and volume in the studied women (p = 0.513).

In the structure of past gynecological diseases, regardless of the course of pregnancy, chronic inflammatory diseases of the pelvic organs (PID) prevailed – 73.4% of cases (p = 0.0213). The remaining women's history was aggravated by abnormal uterine bleeding (8.0%), intraepithelial cervical neoplasia (7.1%), genital endometriosis (0.7%), and polycystic ovary syndrome (0.3%). The analysis data were consistent with the all-Russian structure of gynecological morbidity in women of reproductive age indicating the stable leading position of PID (60-65%), non-inflammatory diseases of the genital tract took second place (21%), benign neoplasms (in the third place – 17%), and abnormal uterine bleeding (the fourth place – 7%) [2].

In Group II patients, pregnancy was aggravated by exacerbations of chronic extragenital diseases and hemodynamic disturbances in the uteroplacental complex which were noted in 58.3% and 89.1% of cases. According to ultrasound, the placental system state showed placenta thinning in 24.7% of women, thrombosis of the intervillous space – in 21.5%, oligohydramnios – in 43%. Medical records of Group II women indicated a high frequency of moderate preeclampsia (33.3%), threatened miscarriages (46.6%), partial chorionic detachment (42.6%), and anemia in pregnant women (58.6%). In 29.2% of pregnant women with placental dysfunction (Group II), an asymmetric form of fetal growth retardation was diagnosed.

In the daily frequency analysis of the time to labor activity onset, a statistically significant relationship to the fetal gender was not revealed (p = 10.069) in any of the clinical groups, apparently due to medical and social factors. However, the labor completion time was significantly associated with the "fetal gender" factor: in the total sample, boys were born 39.4% more often than girls (p = 0.041) associated with a decrease in daily illumination intensity (in the period from 18 to 24 hours); girls were born mainly 35.8% more often with a decrease in illumination intensity (in the morning period from 24 to 6) (p = 0.026).

Depending on the gestation course, the same pattern persisted: in Group I patients, girls were born statistically significantly more often (by 41.2%) (p = 0.019) from 00:00 to 06:00, while the birth of boys was recorded by 25.7% more often in the period from 18:00 to 00:00 hours (p = 0.038). The biorhythm period in the case of both variants of sexual dimorphism was 6 hours.

In clinical Group II, the same pattern persisted: girls were born more often (by 21.6%) in light-saturated hours of the day from 03:00 to 12:00 (the biorhythm period was 9 hours). On the contrary, more boys (by 24.8%) were born as the light-saturated time of day decreased from 16:00 to 00:00 hours (the biorhythm period was 8 hours). The prolongation of the biorhythm period in the case of placental dysfunction is worthy of note.

The regulatory role of melatonin metabolism in maintaining the chronoperiodicity of functional processes has been proven [8, 27], in connection with which the morning 6-SOMT fraction in pregnant clinical groups was analyzed.

It was found that in trimester II in Group I pregnant women regardless of the fetus gender, there was a decrease in 6-SOMT by an average of 31.4% (p = 0.031, p = 0.026) compared with trimester I. In trimester III, compared with trimester II, the 6-SOMT was characterized by an increase: in pregnant women with female fetuses by 3.4 times, with male fetuses by 2.6 times (p = 0.015, p = 0.048), which perhaps is due to the physiological "summation" of maternal, placental, and fetal melatonin (Table 1).

There were no statistically significant differences in the levels of 6-SOMT between Group I pregnant women with different fetus genders during trimesters I and II (p = 0.057, p = 0.062), however, in trimester III, 6-SOMT levels were significantly higher in pregnant women with FFG (p = 0.018).

A somewhat different example was noted in the placental dysfunction group (Group II) of pregnant women: already in the first trimester, 6-SOMT was 25.8% lower than in uncomplicated birth (Group I) regardless of sexual dimorphism (p = 0.041, p = 0.025) (Table 2).

Table 1 / Таблица 1

Levels of 6-sulfatoxymelatonin in the urine of women at different stages of physiological pregnancy, depending on the «sex of the fetus»
Уровни 6-сульфатоксимелатонина в моче пациенток I группы по триместрам гестации в зависимости от фактора «половая принадлежность плода»

Показатель *Index*	Триместры *Trimesters*	Матери девочек n = 280 *Mothers of girls n = 280*	Матери мальчиков n = 304 *Mothers of boys n = 304*
Показатели 6-сульфат-оксимелатонина в моче беременных, нг/мл *6-sulfateoxymelatonin level, ng/ml*	I	78,1[68,6;87,7]•	77,8[67,4;88,1]•
	II	53,5[44,7;62,3]**	56,7[47,3;66,2]**
	III	183,3[174,7;192,3]*/** •	132,7[123,6;142,2]*/**/•

Note: ** — statistical significance of the differences (p < 0.05) in the level of 6-sulfate-oxymelatonin in the subgroups examined in dependence on fetus sex during one trimester; ** — statistical significance of differences in the level of 6-sulfatoxymelatonin in one group in different trimesters of pregnancy; • — statistical significance of differences (p < 0.05) in the level of 6-sulfate-oxymelatonin in the group of the same gender within one trimester between physiological and complicated pregnancy.*
Примечание: * — статистическая значимость отличий (p < 0,05) показателей 6-сульфат-оксимелатонина в моче у беременных клинических групп в течение одного триместра в зависимости от половой принадлежности плода; ** — статистическая значимость отличий показателей 6-сульфатоксимелатонина в моче в одной клинической группе в разные триместры гестации; • — статистическая значимость отличий (p < 0,05) показателей 6-сульфат-оксимелатонинав моче в одноимённой по половой принадлежности группе в пределах одного триместра между физиологическим и осложненным течением беременности.

Table 2 / Таблица 2

Levels of 6-sulfatoxymelatonin in the urine of pregnant women with placental dysfunction depending on the «sex of the fetus»
Уровни 6-сульфатоксимелатонина в моче пациенток II группы по триместрам гестации в зависимости от фактора «половая принадлежность плода»

Показатель *Index*	Триместры *Trimesters*	Матери девочек n = 253 *Mother of girls n = 253*	Матери мальчиков n = 264 *Mothers of boys n = 264*
Показатели 6-сульфат-оксимелатонина в моче беременных, нг/мл *6-sulfateoxymelatonin level, ng/ml*	I	54,4[42,2;66,3]•	53,7[43,4;66,3]•
	II	51,5[39,7;63,5]**	52,7[41,3;64,0]**
	III	125,2[116,0;134,4]*/** •	86,8[77,4;96,3]*/**/•

Note: ** — statistical significance of the differences (p < 0.05) in the level of 6-sulfate-oxymelatonin in the subgroups examined in dependence on fetus sex during one trimester; ** — statistical significance of differences in the level of 6-sulfatoxymelatonin in one group in different trimesters of pregnancy; • — statistical significance of differences (p < 0.05) in the level of 6-sulfate-oxymelatonin in the group of the same gender within one trimester between physiological and complicated pregnancy.*
Примечание: * — статистическая значимость отличий (p < 0,05) показателей 6-сульфат-оксимелатонина в моче у беременных клинических групп в течение одного триместра в зависимости от половой принадлежности плода; ** — статистическая значимость отличий показателей 6-сульфатоксимелатонина в моче в одной клинической группе в разные триместры гестации; • — статистическая значимость отличий (p < 0,05) показателей 6-сульфат-оксимелатонинав моче в одноимённой по половой принадлежности группе в пределах одного триместра между физиологическим и осложненным течением беременности.

In this group, in the pregnancy second trimester, a decrease in 6-SOMT specific to a similar period in uncomplicated birth (Group I) was not revealed. In trimester III, an increase in 6-SOMT was recorded in the case of both fetus gender variants more pronounced in girls' mothers as in the uncomplicated birth case (p = 0.039, p = 0.016).

It should also be noted that in placental dysfunction the absolute values of 6-SOMT were significantly lower compared to the Group I subjects (uncomplicated birth) in

both boys' and girls' mothers (p = 0.024, p = 0.037) which appeared to be due to placental dysfunction.

Analysis of the frequency and structure of complications accompanying the pregnancy and childbirth period in the examined patients showed the following.

In Group II patients, taking into account the "fetal gender" factor, the antiphospholipid syndrome was more often (98.4%) recorded in pregnant women with FFG (p = 0.047). Cervical insufficiency with a comparable frequency was recorded in pregnant women with MFG and FFG was 25.1% and 18.7%, respectively (p = 0.031, p = 0.046).

GDM cases were significantly more frequent (82.8%) in pregnant women with MFG (p = 0.037) than in pregnant women with FFG. A similar pattern was observed when analyzing type 2 diabetes mellitus cases: in pregnant women with MFG, type 2 diabetes mellitus was recorded in 71.3% of cases (p = 0.045). Among fetuses with diabetic fetopathy, boys were also more common (63.6%, p = 0.049), while fetal growth retardation was detected in 63.7% of girls' mothers (p = 0.023).

The occipitoposterior position of the vertex and pre-labor rupture of membranes also prevailed in MFG (78.4% and 53.6%, respectively). When analyzing birth complication in Group II patients, premature detachment of normally situated placenta was more often (in 75.4%) (p = 0.048) detected in women in labor with boys. An unripe cervix was more often diagnosed in pregnant women with FFG (65.7%, p = 0.024).

In the analysis of the state of newborns using the Apgar scale, it was found that the lowest scores (6 points and lower at the 1st minute after birth) were observed in 64.7% of boys (p = 0.023). Fetal macrosomia was found statistically significantly more often (2 times) in mothers of boys (p = 0.031), regardless of the gestation course.

Discussion

The studies carried out indicate that the structural and functional gestational "footprint" formed as a result of a long 9-month mother-fetus interaction modulates the activity of the functional subsystems responsible for the formation of the labor daily frequency. The fetal gender due to the difference in biochemical and mediator signaling determines the differences in the implementation of this period within the "sleep-wakefulness" daily cycle. A statistically significant dependence of the daily cycle acrophases of the labor completion time on the natural illumination intensity was revealed in both physiological and complicated pregnancies: in the male fetus case, the labor completion time is more often shifted to the dark day time with lower 6-SOMT, while the labor completion time in girls' mothers is shifted mainly to the daytime with a higher 6-SOMT compared to boys' mothers. In case of placental dysfunction, a biorhythm period prolongation is registered, which is a manifestation of the chronophysiological compensation of the dysfunctional processes that have arisen in the maternal body: it is known that an increase in biorhythm frequency and decrease in its period, and vice versa, a decrease in frequency and increase in the period of any biorhythm refer to chronophysiological elements of homeostasis maintenance [28, 18].

It is also evident that there is a functional relationship between the regulatory structures responsible for the initiation of the delivery duration in the maternal organism carrying fetuses of different genders and the chrono-regulatory structures, in particular, the epiphysis producing melatonin.

As the delivery date approaches, the MPFFS has four sources of melatonin (pineal gland and internal organs of the mother's body, as well as the placenta and the fetus), which make it possible to achieve its maximum production and ensure maximum mother and fetus adaptation to the delivery. There is also data for the melatonin role as a circadian signal for the onset of labor activity along with oxytocin. As part of the study, it was found that in pregnant women with a female fetus, regardless of the during pregnancy nature, the 6-SOMT was significantly higher. Destructive processes in the placental tissue with placental dysfunction contribute to a decrease in 6-SOMT throughout pregnancy and during childbirth which is a prerequisite for the occurrence of obstetric complications.

Conclusions

The labor completion time in the daily "sleep-wakefulness" cycle regardless of the gestation course is significantly associated with the fetal gender and the natural illumination intensity: in pregnant women with FFG, in the greatest number of cases, the physiological labor completion time is shifted to daylight hours, in the case of MFG – to night-time. The abortion during birth in time in girls' mothers is accompanied by higher melatonin levels since this labor completion time in the case of FFG falls on the period of its greatest production (from 1 a.m. to 3 a.m.). Lower melatonin in mothers of boys, both in the final stages of pregnancy and during childbirth, is apparently due to the functioning of a protective mechanism preserving the male gonads, since high melatonin can have an aggressive effect on testicular theca, up to male infertility in subsequent stages of extrauterine life [29, 30, 8, 22].

Financing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Gratitudes. *The authors are grateful to A.Yu. Ilyin for help in statistical data processing when writing this article.*

Благодарности. Авторы выражают благодарность А.Ю. Ильину за помощь в статистической обработке данных при написании статьи.

ЛИТЕРАТУРА

1. Зайналова С.А., Синчихин С.П., Степанян Л.В. Плацентарная недостаточность - вопросы этиопатогенеза, диагностики, клиники и терапии. // *Астраханский медицинский журнал.* – 2014. – Т.9, №2. – С.15-23. eLIBRARY ID: 21794559
2. Савельева Г.М., Серов В.Н., Сухих Г.Т. *Акушерство и гинекология. Клинические рекомендации.* – Москва: ГЭОТАР-Медиа; 2016.
3. Белоцерковцева Л.Д., Коваленко Л.В., Каспарова А.Э., Сус Л.А. Плацентарная и кардиоплацентарная недостаточность: современные методы функциональной диагностики патологии плода. // *Вестник СурГУ. Медицина.* – 2016. – №2(28). – С.17-23. eLIBRARY ID: 28199173
4. Тапильская Н.И., Мельников К.Н., Кузнецова И.А., Глушаков Р.И. Плацентарная недостаточность и синдром задержки роста плода: этиология, профилактика, лечение. // *Медицинский алфавит.* – 2020. – №4. – С.6-10. DOI: 10.33667/2078-5631-2020-4-6-10
5. Кузнецова Н.Б., Буштырева И.О., Забанова Е.А., Баринова В.В., Гугуева А.В. Прогностическая значимость критических нарушений фетоплацентарного кровотока у беременных с задержкой роста плода. // *Акушерство и гинекология.* – 2020. – №6. – С. 59-64. DOI: 10.18565/aig.2020-6.59-64
6. Di Renzo G.C., Cabero Roura L., Facchinetti F., Helmer H., Hubinont C., et al. Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine. // *Journal of Maternal-Fetal and Neonatal Medicine.* – 2017. – V.30 – №17. – P. –2011-2030. DOI: 10.1080/14767058.2017.1323860
7. Кабанова М.А., Толкач Н.М., Колесникова Н.Б., Калентьева С.В. Течение и исходы беременности в зависимости от пола плода. // *Академический журнал Западной Сибири.* – 2011. – №2. – С.21-23. eLIBRARY ID: 20695501
8. Боташева Т.Л., Хлопонина А.В., Васильева В.В., Заводнов О.П., Каушанская Л.В., Железнякова Е.В. Сезонная периодичность мелатонинового обмена и гормонального статуса беременных в зависимости от пола плода. // *Медицинский вестник Юга России.* – 2018. – Т.9. – №3. – С. 70-76. DOI: 10.21886/2219-8075-2018-9-3-70-76
9. Di Renzo G.C., Rosati A., Sarti R.D., Cruciani L., Cutuli A.M. Does fetal sex affect pregnancy outcome? // *Gend Med.* – 2007. – Vol. 4, № 1. – P. 19-30. DOI: 10.1016/s1550-8579(07)80004-0
10. Ramiro-Cortijo D., de la Calle M., Böger R., Hannemann J., Lüneburg N., et al. Male fetal sex is asso ciated with low maternal plasma anti-inflammatory cytokine profile in the first trimester of healthy pregnancies. // *Cytokine.* – 2020. – 136:155290. DOI: 10.1016/j.cyto.2020.155290.
11. Saoi M., Kennedy K.M., Gohir W., Sloboda D.M., Britz-McKibbin P. Placental Metabolomics for Assessment of Sex-specific Differences in Fetal Development During Normal Gestation. // *Scientific Reports.* – 2020. – V.10. – №1. – 9399. DOI: 10.1038/s41598-020-66222-3.
12. Larsen S.O., Wojdemann K.R., Shalmi A.C., Sundberg K., Christiansen M., Tabor A. Gender impact on first trimester markers in Down syndrome screening. // *Prenat Diagn.* – 2002. – Vol. 22. – P. 1207-1208. DOI: 10.1002/pd.493.
13. Knippel A.J. Role of fetal sex in amniotic fluid alphafetoprotein screening. // *Prenatal Diagnosis.* – 2002. – Vol. 22, Iss.10. – P. 941-945. DOI: 10.1002/pd.408
14. Gol M., Tuna B., Doğan E., Gulekli B., Bagci M., Altunyurt S., et al. Does fetal gender affect cytotrophoblast cell activity in the human term placenta? Correlation with maternal hCG levels. // *Acta Obstet Gynecol Scand.* – 2004. – Vol. 83, № 8. – P. 711-715. DOI: 10.1111/j.0001-6349.2004.00491.x

REFERENCES

1. Zainalova S.A., Sinchikhin S.P., Stepanyan L.V. Placental insufficiency - problems of etiopathogenesis, diagnosis, clinic and treatment. *Astrakhan Medical Journal.* 2014;9(2):15-23. (In Russ.). eLIBRARY ID: 21794559
2. Savel'eva G.M., Serov V.N., Suhih G.T. *Obstetrics and Gynecology. Clinical recommendations.* Moscow: GeOTAR-Media; 2016. (In Russ.).
3. Belotserkovtseva L.D., Kovalenko L.V., Kasparova A. E., Sus L.A. Placental and cardio-placental insufficiency: functional diagnostics modern methods of fetus pathology. *Vestnik SurGU. Medicina.* 2016;2(28):17-23. (In Russ). eLIBRARY ID: 28199173
4. Tapilskaya N.I., Mel'nikov K.N., Kuznetsova I.A., Glushakov R.I. Placental insufficiency and fetal growth restriction: etiology, prevention, and treatment. *Medical alphabet.* 2020;4:6-10. (In Russ). DOI: 10.33667/2078-5631-2020-4-6-10
5. Kuznetsova N.B., Bushtyrova I.O., Zabanova E.A., Barinova V.V., Gugueva A.V. Predictive value of critical disturbances in fetoplacental circulation in intrauterine growth restriction pregnancies. *Obstetrics and Gynecology.* 2020;6:59-64. (In Russ.). DOI: 10.18565/aig.2020-6.59-64
6. Di Renzo GC, Cabero Roura L, Facchinetti F, Helmer H, Hubinont C, et al. Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine. *J Matern Fetal Neonatal Med.* 2017;30(17):2011-2030. DOI: 10.1080/14767058.2017.1323860
7. Kabanova M.A., Tolkach N.M., Kolesnikova N.B., Kalentyeva S.V. The course and outcomes of pregnancy depending on the sex of the fetus. *Academic journal of Western Siberia.* 2011;2:21-23. (In Russ.). eLIBRARY ID: 20695501
8. Botasheva T.L., Khloponina A.V., Vasil'eva V.V., Zavodnov O.P., Kaushanskaya L.V., Zheleznyakova E.V. Seasonal periodicity of melatonin exchange and hormonal status of pregnant women in dependence on fetus sex. *Medical Herald of the South of Russia.* 2018;9(3):70-76. (In Russ.). DOI: 10.21886/2219-8075-2018-9-3-70-76
9. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? *Gend Med.* 2007;4(1):19-30. DOI: 10.1016/s1550-8579(07)80004-0
10. Ramiro-Cortijo D, de la Calle M, Böger R, Hannemann J, Lüneburg N, et al. Male fetal sex is associated with low maternal plasma anti-inflammatory cytokine profile in the first trimester of healthy pregnancies. *Cytokine.* 2020;136:155290. DOI: 10.1016/j.cyto.2020.155290.
11. Saoi M, Kennedy KM, Gohir W, Sloboda DM, Britz-McKibbin P. Placental Metabolomics for Assessment of Sex-specific Differences in Fetal Development During Normal Gestation. *Scientific Reports.* 2020;10(1):9399. DOI: 10.1038/s41598-020-66222-3.
12. Larsen SO, Wøjdemann KR, Shalmi AC, Sundberg K, Christiansen M, Tabor A. Gender impact on first trimester markers in Down syndrome screening. *Prenat Diagn.* 2002;22(13):1207-8. DOI: 10.1002/pd.493
13. Knippel AJ. Role of fetal sex in amniotic fluid alphafetoprotein screening. *Prenat Diagn.* 2002;22(10):941-5. DOI: 10.1002/pd.408.
14. Gol M, Tuna B, Dogan E, Gulekli B, Bagci M, et al. Does fetal gender affect cytotrophoblast cell activity in the human term placenta? Correlation with maternal hCG levels. *Acta Obstet Gynecol Scand.* 2004;83(8):711-5. DOI: 10.1111/j.0001-6349.2004.00491.x
15. Botasheva T.L., Palieva N.V., Khloponina A.V., Vasiljeva V.V., Zheleznyakova E.V., et al. Fetal sex in the development of gestational diabetes mellitus and endothelial dysfunction.

15. Боташева Т.Л., Палиева Н.В., Хлопонина А.В., Васильева В.В., Железнякова Е.В., и др. Пол плода в формировании гестационного сахарного диабета и эндотелиальной дисфункции. // *Акушерство и гинекология*. – 2020. – №9. – С.56-64. DOI: 10.18565/aig.2020.9.56-64
16. Sheiner E., Levy A., Katz M., Hershkovitz R., Leron E., Mazor M. Gender does matter in perinatal medicine. // *Fetal Diagn Ther*. – 2004. – Vol.19, №4. – P.366-369. DOI: 10.1159/000077967
17. Gonzalez T.L., Sun T., Koeppel A.F., Lee B., Wang E.T., et al. Sex differences in the late first trimester human placenta transcriptome. // *Biology of Sex Differences*. – 2018. – Vol. 9, № 4. DOI: 10.1186/s13293-018-0165-y.
18. Агаджанян Н.А. *Основы физиологии человека. Том 1. Нормальная физиология человека*. – М.: РУДН; 2012.
19. Заславская Р.М., Васькова Л.Б., Болсуновская Ю.Р. Хронофармакология и хрономедицина как новый методологический подход к оптимизации лечения. // *Пространство и Время*. – 2012. – №1(7). – С.195-198. eLIBRARY ID: 17322355
20. Ковальзон В.М., Дорохов В.Б. Цикл бодрствование – сон и биоритмы человека при различных режимах чередования светлого и темного периода суток. // *Здоровье и образование в XXI в.* – 2013. – Т.15. – №1-4. – С.151-162. eLIBRARY ID: 20387316
21. Комаров Ф.И., Рапопорт С.И. *Хронобиология и хрономедицина*. – Москва: Триада-Х; 2000.
22. Хлопонина А.В., Боташева Т.Л., Радзинский В.Е., Железнякова Е.В., Заводнов О.П., Бабаян К.Т. Суточная периодичность родов в зависимости от пола плода. // *Вестник Адыгейского государственного университета. Серия естественно-математических наук.* – Майкоп. – 2018. – Вып.3(226). – С.76-83. eLIBRARY ID: 36526536
23. Сидельникова В.М., Сухих Г.Т. *Невынашивание беременности*. – Москва: Мед. информ. агентство (МИА); 2010.
24. Sherer D.M., Kogan M.G. Abnormal nonstress test yet otherwise reassuring biophysical profile in a compromised fetus with severe antepartum intracranial hemorrhage. // *Gynec. Obstet. Invest.* – 2001. – Vol. 52, №1. – P. 66-70. DOI: 10.1159/000052944
25. Двойрин В.В., Клименков А.А. *Методика контролируемых клинических испытаний*. – М: 2004.
26. Боярский А.Я., Громыко Л.Г. *Общая теория статистики*. - М.: Московский университет; 1985.
27. Айламазян Э.К., Евсюкова И. И., Ярмолинская М. И. Роль мелатонина в развитии гестационного сахарного диабета. // *Журнал акушерства и женских болезней*. – 2018. – Т.67, №1. – С.85-91. DOI: 10.17816/JOWD67185-91
28. Загускин С.Л. *Ритмы клетки и здоровье человека*. – Ростов н/Д: ЮФУ; 2010.
29. Чехонацкая М.Л., Василевич Л.К., Бондаренко Н.А. Влияние особенностей течения беременности на формирование яичек плода (обзор). // *Саратовский научно-медицинский журнал*. – 2013. – Т.9, №2. – С.234-240. eLIBRARY ID: 20203827
30. Комаров Ф.И., Рапопорт С.И., Бреус Т.К., Чибисов С.М. Десинхронизация биологических ритмов как ответ на воздействие факторов внешней среды. // *Клиническая медицина*. – 2017. – Т.95, №6. – С.502-512. DOI: 10.18821/0023-2149-2017-95-6-502-512

Информация об авторах

Боташева Татьяна Леонидовна, д.м.н., проф., главный научный сотрудник отдела медико-биологических проблем в акушерстве, гинекологии и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0001-5136-1752. E-mail: t_botasheva@mail.ru.

Obstetrics and Gynecology. 2020;9:56-64. (In Russ.). DOI: 10.18565/aig.2020.9.56-64
16. Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. *Fetal Diagn Ther.* 2004;19(4):366-9. DOI: 10.1159/000077967
17. Gonzalez TL, Sun T, Koeppel AF, Lee B, Wang ET, et al. Sex differences in the late first trimester human placenta transcriptome. *Biol Sex Differ*. 2018;9(1):4. DOI: 10.1186/s13293-018-0165-y
18. Agadzhanyan N.A. *Fundamentals of human physiology. Volume 1. Normal human physiology*. Moscow .: RUDN; 2012. (In Russ.).
19. Zaslavskaya R.M., Vas'kova L.B., Bolsunovskaya Y.R. Chronopharmacology and chronomedicine as a new methodological approach to optimize the therapy. *Space and time.* 2012;1(7):195-198. (In Russ.). eLIBRARY ID: 17322355
20. Kovalzon V.M., Dorokhov V.B. Human sleep-waking cycle and biorhythms with the different regimens of natural light-dark alternation. *Health and education in the XXI century.* 2013;15(1-4):151-162. (In Russ.). eLIBRARY ID: 20387316
21. Komarov F.I., Rapoport S.I. *Chronobiology and chronomedicine*. Moscow: Triada-X; 2000. (In Russ.).
22. Khloponina A.V., Botasheva T.L., Radzinsky V.E., Zheleznyakova E.V., Zavodnov O.P., Babayan K.T. Daily periodicity of labor depending on fetus sex. *The Bulletin of the Adyghe State University*. 2018;3(226):76-83. (In Russ.). eLIBRARY ID: 36526536
23. Sidelnikova V.M., Sukhikh G.T. *Miscarriage*. Moscow: Honey. inform. agency (MIA); 2010. (In Russ.).
24. Sherer DM, Kogan MG. Abnormal nonstress test yet otherwise reassuring biophysical profile in a compromised fetus with severe antepartum intracranial hemorrhage. *Gynecol Obstet Invest*. 2001;52(1):66-70. DOI: 10.1159/000052944
25. Dvoirin V.V., Klimenkov A.A. *Methodology of controlled clinical trials.* Moscow. 2004. (in Russ.).
26. Boyarsky A.Ya., Gromyko L.G. *General theory of statistics.* Moscow: Moscow University; 1985. (In Russ.).
27. Aulamazyan E.K., Evsyukova I.I., Yarmolinskaya M.I. The role of melatonin in development of gestational diabetes mellitus. *Journal of Obstetrics and Women's Diseases*. 2018;67(1):85-91. (In Russ.). DOI: 10.17816/JOWD67185-91
28. Zaguskin S.L. *Cell rhythms and human health.* Rostov on Don: SFU; 2010. (In Russ.).
29. Chekhonatskaya M.L., Vasilevich L.K., Bondarenko N.A. Influence of pregnancy course peculiarities on formation of fetal testicles (review). *Saratov Journal of Medical Scientific Research*. 2013;9(2):234-240. (In Russ.). eLIBRARY ID: 20203827
30. Komarov F.I., Rapoport S.I., Breus T.K., Chibisov S.M. Desynchronization of biological rhythms in response to environmental factors. *Clinical medicine.* 2017;95(6):502-512. (In Russ.). DOI: 10.18821/0023-2149-2017-95-6-502-512

Information about the authors

Tatyana L. Botasheva, Dr. Sci. (Med.), Professor, Chief Researcher, Department of Biomedical Problems in Obstetrics, Gynecology and Pediatrics Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0001-5136-1752. E-mail: t_botasheva@mail.ru.

Андреева Вера Олеговна, д.м.н., доцент, главный научный сотрудник акушерско-гинекологического отдела, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-7534-134X. E-mail: vandreyeva@mail.ru.

Лебеденко Елизавета Юрьевна, д.м.н., профессор кафедры акушерства и гинекологии №3, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0003-2602-1486 E-mail: lebedenko08@mail.ru.

Фабрикант Анна Дмитриевна, ординатор кафедры Акушерства и гинекологии №1 Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-4376-8111 E-mail: annutka944@mail.ru.

Хлопонина Анна Валерьевна, д.м.н., старший научный сотрудник акушерско-гинекологического отдела Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-2056-5231. E-mail: annakhloponina@yandex.ru.

Железнякова Елена Васильевна, к.м.н., научный сотрудник отдела медико-биологических проблем в акушерстве, гинекологии и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0003-4496-6387. E-mail: elena.Gel.1961@yandex.ru.

Заводнов Олег Павлович, к.б.н., научный сотрудник отдела медико-биологических проблем в акушерстве, гинекологии и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: https://orcid.org/0000-0002-9555-2267. E-mail: ozz2007@mail.ru.

Vera O. Andreeva, Dr. Sci. (Med.), Associate Professor, Chief Researcher, Obstetrics and Gynecology Department, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-7534-134X. E-mail: vandreyeva@mail.ru.

Elizaveta Yu. Lebedenko, Dr. Sci. (Med.), Professor of the Chair of obstetrics and gynecology №3, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0003-2602-1486 E-mail: lebedenko08@mail.ru.

Anna D. Fabrikant, Resident of the Department of Obstetrics and Gynecology No. 1, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-4376-8111 E-mail: annutka944@mail.ru.

Anna V. Khloponina, Dr. Sci. (Med.), Senior Researcher, Obstetric and Gynecological Department, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-2056-5231. E-mail: annakhloponina@yandex.ru.

Elena V. Zheleznyakova, Cand. Sci. (Med.), Research Associate, Department of Biomedical Problems in Obstetrics, Gynecology and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0003-4496-6387 E-mail: elena.Gel.1961@yandex.ru.

Oleg P. Zavodnov, Dr. Sci. (Bio.), , Researcher, Department of Biomedical Problems in Obstetrics, Gynecology and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-9555-2267 E-mail: ozz2007@mail.ru.

Вклад авторов

Т.Л. Боташева, Е.Ю. Лебеденко — написание текста рукописи;

В.О. Андреева — разработка дизайна исследования;

А.Д. Фабрикант, Е.В. Железнякова — обзор публикаций по теме статьи;

А.В. Хлопонина, О.П. Заводнов — получение и анализ данных.

Authors contribution

T.L. Botasheva, E.Yu. Lebedenko — writing the text of the manuscript;

V.O. Andreeva — research design development;

A.D. Fabricant, E.V. Zheleznyakova — review of publications on the topic of the article;

A.V. Khloponina, O.P. Zavodnov — obtaining and analysis of the data.

Получено / Received: 02.02.2021
Принято к печати / Accepted: 09.02.2021

УДК: 618.4-07:618.5-089.888.61
DOI 10.21886/2219-8075-2021-12-1-54-61

Opportunities for predicting cesarean scar insufficiency

M.V. Galustyan, I.I. Kutsenko, I.O. Borovikov, A.S. Magay

Kuban State Medical University, Krasnodar, Russia

Objective. The study aimed to compare the diagnostic value of different methods of assessing the condition of the scar on the uterus after a cesarean section. **Materials and methods.** A comparative analysis of the diagnostic value of assessing the validity of the scar on the uterus in the pre-graviridar period and during pregnancy ultrasound (ultrasound) investigation with dopplerometry (DM), magnetic resonance imaging (MRI), and microwave radiothermometry (RTM). The study included fertile patients after delivery by cesarean section (n = 56), at the planning stage, during pregnancy and after delivery, both through natural birth pathways and by re-cesarean section. **Results.** A comparative analysis of the assessment of the scar in the uterus by the mentioned methods revealed the comparable diagnostic value of these methods during the planning phase of pregnancy and in gestation time 11–12 and 20 –21 weeks, while at the period of 37–38 weeks, the sensitivity of RTM was significantly (1.6 times) higher than ultrasound investigation. **Conclusions.** Despite the high diagnostic effectiveness of all three methods of assessing the condition of the uterine scar after cesarean section, the method of microwave radiothermometry has advantages in the simplicity of the method, lack of need for expensive equipment, and specialized qualifications of the doctor.

Keywords: cesarean section, uterine scar, ultrasound, magnetic resonance imaging, microwave radiothermometry.

For citation: Galustyan M.V., Kutsenko I.I., Borovikov I.O., Magay A.S. Opportunities for predicting cesarean scar insufficiency. *Medical Herald of the South of Russia.* 2021;12(1):54-61. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-54-61.

Corresponding author: Marina V. Galustyan, doctor.mar@mail.ru.

Возможности прогнозирования несостоятельности рубца на матке после операции кесарева сечения

М.В. Галустян, И.И. Куценко, И.О. Боровиков, А.С. Магай

Кубанский государственный медицинский университет, Краснодар, Россия

Цель: сравнить диагностическую ценность различных методов оценки состояния рубца на матке после операции кесарева сечения. **Материалы и методы:** проведён сравнительный анализ диагностической ценности оценки состоятельности рубца на матке в предгравидарном периоде и во время беременности ультразвукового исследования (УЗИ) с допплерометрией (ДМ), магнитно-резонансной томографии (МРТ) и микроволновой радиотермометрии (РТМ). Материалом исследования послужили фертильные пациентки после родоразрешения путем операции кесарева сечения (n = 56) на этапе планирования, во время беременности и после родоразрешения как через естественные родовые пути, так и путём повторного кесарева сечения. **Результаты:** сравнительный анализ оценки состоятельности рубца на матке тремя способами выявил сопоставимую диагностическую ценность этих методов на этапе планирования беременности и в сроке гестации 11–12 и 20–21 недель, при этом на сроке 37–38 недель чувствительность РТМ была достоверно (в 1,6 раза) выше, чем УЗИ. **Заключение:** несмотря на достаточно высокую диагностическую эффективность всех трёх методов оценки состояния рубца на матке после операции кесарева сечения, метод микроволновой радиотермометрии имеет преимущества в легкости выполнения, отсутствии необходимости в дорогостоящем оборудовании и специализированной квалификации врача.

Ключевые слова: кесарево сечение, рубец на матке, ультразвуковое исследование, магнитно-резонансная томография, микроволновая радиотермометрия.

Для цитирования: Галустян М.В., Куценко И.И., Боровиков И.О., Магай А.С. Возможности прогнозирования несостоятельности рубца на матке после операции кесарева сечения. *Медицинский вестник Юга России.* 2021;12(1):54-61. DOI 10.21886/2219-8075-2021-12-1-54-61.

Контактное лицо: Галустян Марина Вадимовна, doctor.mar@mail.ru.

Introduction

In modern obstetrics, cesarean section is the most widespread assisted delivery surgery (in the Russian Federation, the rate is 15–16% on average, reaching 30-40% in 3rd-level obstetrics centers – perinatal centers) [1–4]. The number of extragenital pathologies and patients with burdened gynecologic-obstetrical anamnesis (especially, infertile patients after assisted reproductive treatment and age primipara, and patients with combined endocrine pathology) is increasing among the indications for cesarean section [4, 5]. The above-mentioned factors contribute to an increase in the number of abdominal deliveries and contribute to the increase in women with a uterine scar, which is the main indication for the repeated cesarean section in nearly all countries [1–4]. At the same time, the number of complications during a repeated cesarean section increases by 3–4 times, which is more than 20% (5 times higher than after the first cesarean section [2–4]. A hysterectomy injury associated with operative delivery leads to a disturbance of intrauterine hemostasis and uterine drainage, which increases the rate of hemorrhagic and purulent-septic complications [5]. Besides, there are some unfavorable prognoses for complete recovery after abdominal delivery that include the increased risk of gynecological diseases (endometriosis, secondary infertility, syndrome of pelvic pains), subsequent obstetrical complications (ectopic pregnancy, premature delivery, fetal presentation, and placenta increta) [1, 5–7].

The rationale for the present study is defined by the factors that can in the future provide possible vaginal delivery after assisted surgical delivery in the anamnesis, which requires the establishment of significant and reliable criteria for scar competence. Presently, obstetrician-gynecologists have two opinions regarding conservative vaginal delivery in patients with a uterine scar. Some specialists believe that vaginal delivery in such patients contributes to a decrease in the rate of caesarian sections, and thus, the rate of associated complications [2]. Others highlight the impossibility to standardize the criteria of uterine scar competence, which will increase the rate of metrorrhexis along the scar [1, 2]. Despite this diversity in opinions, presently, more and more clinical studies appear that focus on different methods of pregnancy and delivery management in women with a uterine scar that would provide successful vaginal delivery [4–9]. Even though there is a high rate of repeated abdominal deliveries at the majority of neonatal centers in Russia and the world, the so-called "careful approach" to the choice of the method of delivery in patients with a uterine scar, more and more institutions (primarily of the level III) practice vaginal delivery in such patients [10].

Primarily, the possibility of conservative delivery in women with a uterine scar after cesarean section is determined by the quality of the morphofunctional healing of the lower uterine segment, which requires the search for reliable methods of evaluation of uterine scar competence [11, 12]. Presently, the most widespread method of the evaluation of the uterine scar is the ultrasonic investigation of the uterine scar in the pre-conceptional period and during pregnancy (evaluation of the thickness of the lower uterine segment, consistency of the myometrium in the scar area, acoustic density in the area of the former section). Besides, a complex examination of the uterine scar is becoming more popular before pregnancy (ultrasonography (US) with a contrasting agent, hysterography with contrasting agent, hysteroscopy, biopsy with further histological study, computed tomography (CT), and magnetic resonance imaging (MRI)) [11–13]. Even though the majority of these studies provide quite reliable information on the regeneration of the uterine scar, there are no precise criteria on the uterine scar competence evaluation and there is no objective algorithm for the determination of the possibility of vaginal delivery for such women.

Apart from clinical and anamnestic signs of the uterine scar incompetence, modern clinical recommendations include ultrasound investigation during pregnancy (indirect signs of the uterine scar incompetence include the thickness of the lower segment less than 2 and more than 5 mm, incompetence of the lower segment in the scar area (balloon-shaped, cone-shaped lower segment), the symptom of the "niche", and increased acoustic density along the former section. Still, a decision on the uterine scar competence can be made intraoperatively only during cesarean section with its visual evaluation or after vaginal delivery (manual examination of the uterine cavity) [11–13].

The method of microwave radio thermometry (RTM), i.e. the measurement of the intensity of electromagnetic radiation of the human tissues in the range of super-high frequency for the evaluation of the uterine scar competence after a cesarean section is a new and promising method that has not been applied before in this area. A change in tissue temperature can be caused by inflammatory changes in the wounded tissues or their incompetence associated with the regeneration in this area. Besides, the absolute safety of RTM for patients and personnel should be noted. All the above-mentioned provides the rationale for the present study.

The study aimed to perform a comparison of the diagnostic value of different methods of evaluation of the uterine scar competence after abdominal delivery.

Materials and Methods

The studies were performed at the facilities of Kuban State Medical University of the Ministry of the Russian Federation at the Department of Obstetrics, Gynecology, and Perinatology (Head of the Department Prof. Kutsenko, PhD). A prospective, non-randomized study was performed at the perinatal center of Krasnodar Regional Clinical Hospital for Children (January 2018 – August

2019). The study included 56 fertile women who had abdominal delivery not later than 18 months before the study, were included in the study during the pre-conception period, and had a successful delivery. The examination was performed according to the Decree No. 572n dated November 12, 2012 of the Ministry of Healthcare of the Russian Federation. The study was approved by the local ethical committee Protocol No. 4 dated September 23, 2019.

Criteria of inclusion in the study:

- age 18 years old and older;
- one uterine scar after cesarean section in the lower uterine segment (the surgery was performed not later than 18 months before the study). The surgery was performed in the 37th week of pregnancy and later (single fetation). Uncomplicated post-operative period;
- lack of severe somatic pathology and malignant neoplasms;
- lack of other absolute and relative indications to abdominal delivery;
- signed form of informed consent for participation in the study.

Apart from a general clinical study (Decree No. 572n), the methods of instrumental diagnostics of the uterine scar competence after a cesarean section included transvaginal ultrasound scanning and power Doppler, MRI, and microwave RTM. US criteria of uterine scar competence included the thickness of myometrium in the area of the lower uterine segment, typicality of the scar location, lack of deformities, "niches", areas of retraction, lack of fibrous inclusions and liquid structures in the scar, blood feeding, and the condition of the retrouterine space. MRI criteria included the lack of local niche-like thinning of the myometrium.

The method of RTM (diagnostic complex RTM-01-RES, Russia) included the measurement of the internal myometrium temperature in the area of the uterine scar and the temperature of the skin and subcutaneous adipose tissue of the anterior abdominal wall. The study was performed in the supine position on a standard gynecological examination chair. The measurements were made in 3 points by a transabdominal sensor and in 3 points – by a transvaginal sensor. An antenna for receiving electromagnetic waves was applied to the studied point on the anterior abdominal wall and vaginally until the current temperature values were received. After the measurement of the internal temperature, the temperature was measured on the skin at the same points. The obtained results were analyzed. The RTM study of the myometrium in the area of the uterine scar revealed the most hypo- and hyperthermal areas along the scar, thermal asymmetry, and dispersion of the temperature. The results were presented as a graph (horizontal axis – points of measurements, vertical axis – temperature values) to evaluate the difference of temperatures in the area. To make a graphic image of a thermogram, a method of color visualization of thermal fields on the screen was used. The performed studies allowed the authors to identify the index of thermal asymmetry (ITA) as a ratio of hyper- and hypothermal areas of the myometrium. This method provides increased precision and objectivity of evaluation of the uterine scar competence. At the stage of studies, a great number of thermograms obtained from patients with cesarean section revealed 3 typical features that were formalized by the following factors:

1. Maximum temperature values in the area of the uterine scar in comparison with the average temperature tsc – tav, where tav = ∑6ti/6, ti — the temperature in 6 points (3 – transabdominal, 3 – transvaginal).

2. The mean quadratic difference of temperatures between the points in the uterine scar √∑6ti2/6 was compared in points 0…6.

3. Index of thermal asymmetry: ITA = (Tmax – Tmin); where Tmax is the maximum temperature in the uterine scar area, Tmin — the minimum temperature in the area of the uterine scar (3 transabdominal, 3 – transvaginal). When the ITA exceeds 0.9, this indicates an increased thermal asymmetry, which can be a sign of the uterine scar incompetence.

If the study is based on one parameter, the sensitivity of the method will be 60–75%. When all the features are considered, the sensitivity increases to 90% with the specificity not less than 85%.

The study design included 4 visits: visit 1 (pre-conception period) – informed consent, anamnesis, complex clinical study, evaluation of the uterine scar outside pregnancy (US, MRI, and RTM); visits 2, 3, and 4 (11th–12th, 20th–21st, and 37th–38th week of pregnancy) – evaluation of the uterine scar during pregnancy (US and RTM); visit 5 (conservative/abdominal delivery) – visual and clinical evaluation of the uterine scar.

The obtained results were included in the statistical analysis with the calculation of the mean arithmetic value (M), the standard of the mean (m), and a statistically significant difference between the parameters (P) using the Student-Fisher test and Statistica 6.0.

Results

The study included 56 women aged 23–35 years old (mean age 28.3 ± 4.7 years old) who were examined and successfully delivered with one uterine scar after the cesarean section. The interval between the previous surgery and the first visit was 22.4 ± 2.9 months. Anamnestic cesarean section was performed as a planned (11/56 – 19.6%) and urgent surgery (45/56 – 80.4%). The majority of operations were performed intranatally (31/56 – 55.4%). Anamnestic data on the previous operations were obtained from patients and delivery records from obstetrics centers. Primarily, these records did not contain the peculiarities

of the surgery and post-operative period (43/56 – 76.8%). The collected anamnesis allowed the authors to reveal the peculiarities of previous pregnancies, indications to abdominal delivery, and the post-operative period. It was impossible to obtain the data on the method of the uterine section suturing and the used suturing material.

Discussion

The mean age of the first pregnancy of patients was 21.4 ± 3.7 years old, the age of the first delivery was 26.1 ± 3.4 years old. Spontaneous miscarriage and missed miscarriage were registered in 7.1% (4/56) women, ectopic pregnancy was registered in 7.1% (4/56), which did not exceed the general population values. In the other parameters, there were no differences from the mean statistical values (Table 1).

Indications for cesarean section in the patients were divided into the following groups (Letter of the Ministry of Healthcare of the Russian Federation dated May 6, 2014 No. 15-4/10/2-3190; Bezhenar, 2019) (Table 2):

The most frequent indications for abdominal delivery were fetal distress in 37.5% (21/56) and abnormalities in the contractive activity of the uterus in 19.6% (11/56).

Table 1 / Таблица 1

Patient parity (n = 56)
Паритет пациенток (n = 56)

Количество родов / *Number of births*					
1		2		3	
n	%	n	%	n	%
49	83,0	6	10,7	1	1,8
Аборт (артифициальный) *Abortion (artificial)*		Аборт (самопроизвольный) *Abortion (self-involuntary)*		Эктопическая беременность *Ectopic pregnancy*	
n	%	n	%	n	%
8	14,3	4	7,1	2	3,6

Table 2 / Таблица 2

Anamnestic evidence for abdominal delivery (n = 56)
Анамнестические показания к абдоминальному родоразрешению (n = 56)

Показания / *Indications*	n	%
Предлежание плаценты / *Placenta praevia*	2	3,6
Преждевременная отслойка нормально расположенной плаценты / *Premature detachment of normally located placenta*	4	7,1
Неправильное положение и предлежание плода / *Wrong position and fetal prejudging*	7	12,5
Пролонгированная / переношенная беременность / *Prolonged / premature pregnancy*	5	8,9
Плодово-тазовая диспропорция / *Fetal-pelvic disproportion*	3	5,4
Анатомические препятствия в родах / *Anatomical obstacles in childbirth*	0	0,0
Угрожающий разрыв матки / *Threatening rupture of the uterus*	1	1,8
Тяжёлая преэклампсия / *Severe pre-eclampsia*	2	3,6
Дистресс плода / *Fetal distress*	21	37,5
Аномалии сократительной деятельности матки / *Abnormalities in the contractile activity of the uterus*	11	19,6
Соматическая патология, исключающая потуги / *Somatic pathology that excludes extinguishes*	0	0,0
Предыдущие операции на матке / *Previous uterus surgeries*	0	0,0

Ultrasound examination of patients in the pre-conception period showed the following results: the thickness of the uterine scar outside pregnancy ≥ 5.0 mm was revealed in 51/56 (91.1%) patients, the symptom of "niche" – in 2/56 (3.6%) women who planned pregnancy, increased acoustic density in the area of the former section — in 4/56 (7.1%) patients. MRI confirmed the obtained data. The thinning of the lower segment of the uterus < 4.3 mm was revealed in 5/56 (8.9%) women, the "niche" was confirmed in 2/56 (3.6%) patients. RTM revealed that the mean ITA in the studied group was 0.75 ± 0.13; in 4/56 women, it exceeded the threshold (mean value of ITA was 1.24 ± 0.41), which is an indirect sign of uterine scar incompetence (Figure 1).

A comparison of these three studies (US, MRI, and RTM) did not reveal any differences in their diagnostic value. The signs of the uterine scar incompetence (thinning of the lower segment, "niche", thermal asymmetry) were detected in the same patients, four of them required further hysteroscopy for the verification of the diagnosis, three of them later underwent metroplasty, which was a criterion for the withdrawal from the study. The remaining 53 patients conceived with further embryo development within 34.2 ± 9.6 weeks after a pre-conception preparation. Taking into account that MRI during pregnancy is made only when medically strictly required, further comparison of the diagnostic value of methods was made between US and RTM in the screening dates (11th–12th and 20th–21st weeks) and full-term pregnancy (37th–38th weeks).

In weeks 11–12 of pregnancy, US of the lower uterine segment in 53 pregnant women revealed an average thickness of the scar 4.1 ± 0.8 mm (in 2/53 (3.8%) patients, the thickness of the scar was not less than 2.0 mm), the "niche" was not revealed in any patients. At this stage of pregnancy, the average ITA was 0.79 ± 0.14 (in 3/53 (5.7%) women, ITA was > 0.90). Despite indirect signs of thinning of the uterine wall in the area of the uterine scar in 2 patients and its inconsistency in 3 patients, the pregnancies were successfully preserved. The study performed in weeks 20–21 of pregnancy showed similar results: the mean thickness of the uterine scar was 3.8 ± 0.7 mm with the lack of "niches" in all the pregnant women. At this stage, the average ITA was 0.81 ± 0.17. Indirect signs of uterine scar incompetence were revealed in the same 3/53 (3.8%) patients.

In the case of full-term pregnancies (37–38 weeks), the results of the two methods of the study significantly differed. The mean thickness of the lower uterine segment in the area of the uterine scar in pregnant decreased by 2 times and was 2.3 ± 0.8 mm. At the same time, in 12/53 (22.6%) of patients, a thinning of the uterine scar was less than 2.0 mm, and in 5/53 (9.4%), a "niche" was revealed. The data obtained by RTM showed that at this stage of gestation, the mean ITA was 0.84 ± 0.16. Thermal asymmetry that exceeded the threshold values (0.9) was registered in 19/53 (35.8%) pregnant (Figure 2). In other words, at full-time pregnancy, RTM revealed indirect signs of uterine incompetence 1.6 times more often than US.

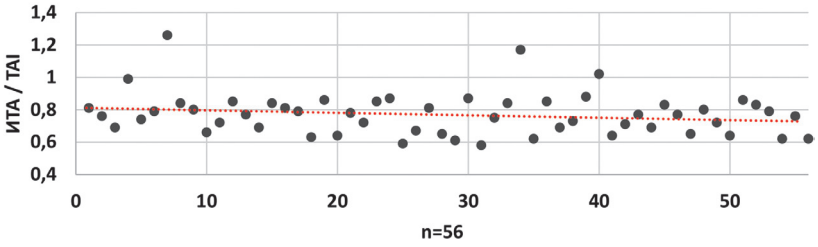

Figure 1. Patient thermoassymetry index (pre-gravity training).
Рисунок 1. Индекс термоассиметрии пациенток (предгравидарная подготовка).

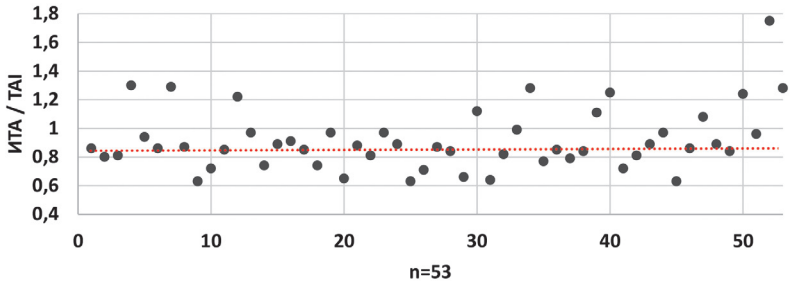

Figure 1. Patient thermoassymetry index (pre-gravity training).
Рисунок 1. Индекс термоассиметрии пациенток (предгравидарная подготовка).

Table 3 / Таблица 3

Evidence for abdominal delivery (n = 41)
Показания к абдоминальному родоразрешению (n = 41)

Показания / *Indications*		
Плановые / *Planned*	n	%
Несостоятельность рубца на матке / *Insolvent scar on the uterus*	13	31,7
Неправильное положение и предлежание плода / *Wrong position and fetal prejudging*	1	2,4
Отсутствие биологической готовности к родам / *Lack of biological readiness for childbirth*	4	9,8
Крупный плод / *Large fetal*	2	4,8
Плацентарная недостаточность / *Placental insufficiency*	1	2,4
Отказ от консервативных родов / *Abandoning conservative childbirth*	3	7,3
Экстренные / *Emergency*	n	%
Плодово-тазовая диспропорция / *Fetal-pelvic disproportion*	1	2,4
Угрожающий разрыв матки / *Threatening rupture of the uterus*	4	9,8
Тяжелая преэклампсия / *Severe pre-eclampsia*	1	2,4
Дистресс плода / *Fetal distress*	4	9,8
Аномалии сократительной деятельности матки / *Abnormalities in the contractile activity of the uterus*	6	14,6
Преждевременная отслойка нормально расположенной плаценты / *Premature detachment of normally located placenta*	1	2,4

The next stage for all the patients was delivery. Abdominal delivery was observed in 41/53 (77.4%) patients. Out of them, the planned surgery was in 24/53 (45.3%) cases, the rest underwent antenatal (6/53 (11.3%)) and intranatal abdominal delivery (11/53 (20.7%)). The indications for the planned and urgent abdominal delivery are presented in Table 3.

The most frequent indication for the planned abdominal delivery was the presence of clinical and functional signs of the uterine scar incompetence (13/53 (24.5%)). At the same time, intraoperatively, this diagnosis was confirmed in 100% of cases (thinning and defects of the muscular tissues in the area of the uterine tissue, which required metroplasty). Among urgent indications for cesarean section, there were abnormalities of contractive activity of the uterus (6/53 (11.3%)), threatening rupture of the uterus, and fetal distress 4/53 (7.5% each).

Besides, it should be mentioned that in 5/53 (9.4%) cases, the uterine scar incompetence was revealed during surgery, i.e. the number of incompetent uterine scars was 18/53 (34.0%).

Thus, the evaluation of the uterine scar competence in the pre-conception period by the three methods (US, MRI, and RTM) was comparable by sensitivity and specificity. In the case of full-time pregnancy, the evaluation of the uterine scar competence revealed a higher sensitivity of RTM diagnostics. Besides, this method does not require specific training and narrow specialization of a doctor (4-hour training). The apparatus is portable, compact, and economically more beneficial.

Finansing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Мудров В.А., Мочалова М.Н., Мудров А.А. Особенности родоразрешения беременных с рубцом на матке через естественные родовые пути на современном этапе. // *Журнал акушерства и женских болезней*. – 2018. – Т.67(1). – С.26–37. DOI: 10.17816/JOWD67126-37.
2. Жуковский Я.Г. Кесарево сечение в XXI веке: новые ответы. О парадигме безопасности для врача и пациентки. // *Status Praesens*. – 2012. - №1(07). – С. 32–36. eLIBRARY ID: 28340447
3. Костин И.Н., Лаврова Н.Ю., Князев С.А., Смирнова Т.В., Кузнецова О.А. Интранатальные факторы риска и неонатальные исходы. // *Вестник РУДН. Серия Медицина*. – 2010. - №6. – С. 71-75.
4. Wood S., Cooper S., Rossa S. Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with intact membranes. // *BJOG*. – 2014. – V.121(6). – P. 674-685. DOI: 10.1111/1471-0528.12328
5. Ananth C., Vintzileos A. Trends in cesarean delivery for pregnancy and association with perinatal mortality. // *Am. J. Obstet. Gynecol*. - 2011. – V.204(6). – P. 505.e1-8. DOI: 10.1016/j.ajog.2011.01.062.
6. Мартынов С.А. Дефект рубца на матке после кесарева сечения: диагностика и лечение вне беременности. // *Гинекология*. – 2020. - №22(3). – С.6-10. DOI: 10.26442/20795696.2020.3.200189.
7. Кесова М.И., Болотова О.В., Кан Н.Е., Орджоникидзе Н.В. Прогностические критерии оценки состояния рубца на матке после кесарева сечения. // *Вестник Российского университета дружбы народов. Серия «Медицина»*. – 2009. - №5. – С.175-180.
8. Шалашова Ю.В. К вопросу о психологических проблемах женщин, родивших с помощью кесарева сечения. // *Сибирский психологический журнал*. - 2001. - №14. – С.72-73. eLIBRARY ID: 26002197
9. Menacker, F., Declercq E., Macdorman M.F. Cesarean delivery: background, trends, and epidemiology. // *Semin Perinatol*. – 2006. – V.30(5). – P.235-41. DOI: 10.1053/j.semperi.2006.07.002.
10. Gao L., Huang Z., Zhang X., Zhou N., Huang X., Wang X. Reproductive outcomes following cesarean scar pregnancy – a case series and review of the literature. // *Eur J Obstet Gynecol Reprod Biol*. – 2016. – V.200. – P.102-107. DOI: 10.1016/j.ejogrb. 2016.02.039.
11. Ножницева О.Н., Семенов И.А., Беженарь В.Ф. Рубец на матке после операции кесарева сечения и оптимальный алгоритм диагностики его состояния. // *Лучевая диагностика и терапия*. - 2019. - №2. – С.85-90. DOI: 10.22328/2079-5343-2019-10-2-85-90
12. Setubal A., Alves J., Osório F., Guerra A., Fernandes R, et al. Treatment for Uterine Isthmocele, A Pouchlike Defect at the Site of a Cesarean Section Scar. // *J Minim Invasive Gynecol*. - 2018. – V.25(1). – P.38-46. DOI: 10.1016/j.jmig.2017.09.022.
13. Ножницева О.Н., Беженарь В.Ф. Ниша рубца на матке после кесарева сечения – новая проблема репродуктивного здоровья женщины. // *Журнал акушерства и женских болезней*. – 2020. - Т69(1). – С.53-62. DOI: 10.17816/JOWD69153-62

Информация об авторах

Галустян Марина Вадимовна, аспирант кафедры акушерства, гинекологии и перинатологии Кубанский государственный медицинский университет, Краснодар, Россия,. ORCID: 0000-0002-0448-7923. E-mail: doctor.mar@mail.ru.

REFERENCES

1. Mudrov V.A., Mochalova M.N., Mudrov A.A. Features of women's vaginal delivery with uterine scar at present stage. *Journal of Obstetrics and Women's Diseases*. 2018;67(1):26-37. (In Russ.). DOI: 10.17816/JOWD67126-37.
2. Zhukovskiy Y.G. C-section in the 21st century: new answers. *Status Praesens.* 2012;1(07):32-36. (In Russ.). eLIBRARY ID: 28340447
3. Kostin I.N., Lavrov A.Y., Knyazev S.A., Smirnova T.V., Kuznetsova O.A. Intranatal risk factors and neonatal outcomes. *Herald RUDN. The series Medicine*. 2010;(6):71-75. (In Russ.)
4. Wood S, Cooper S, Ross S. Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with intact membranes. *BJOG.* 2014;121(6):674-85; discussion 685. DOI: 10.1111/1471-0528.12328
5. Ananth CV, Vintzileos AM. Trends in cesarean delivery at preterm gestation and association with perinatal mortality. *Am J Obstet Gynecol.* 2011;204(6):505.e1-8. DOI: 10.1016/j.ajog.2011.01.062.
6. Martynov S.A. Cesarean scar defects: diagnosis and treatment in non-pregnant women. *Gynecology.* 2020;22(3):6-10. (In Russ.). DOI: 10.26442/20795696.2020.3.200189
7. Kesova M.I., Bolotova O.V., Kan N.Y., Ordjonikidze N.V. Prognostic criteria of the cesarean scar status appraisal. *RUDN Journal of Medicine.* 2009;(5):175-180. (In Russ.).
8. Shalashova Y.V. To the question of the psychological problems of women who have given birth by caesarean section. *Siberian Journal of Psychology*. 2001;(14-15):72-73. (In Russ.). eLIBRARY ID: 26002197
9. Menacker F, Declercq E, Macdorman MF. Cesarean delivery: background, trends, and epidemiology. *Semin Perinatol.* 2006;30(5):235-41. DOI: 10.1053/j.semperi.2006.07.002.
10. Gao L, Huang Z, Zhang X, Zhou N, Huang X, Wang X. Reproductive outcomes following cesarean scar pregnancy - a case series and review of the literature. *Eur J Obstet Gynecol Reprod Biol.* 2016;200:102-7. DOI: 10.1016/j.ejogrb.2016.02.039
11. Nozhnitseva O.N., Semenov I.A., Bezhenar V.F. The scar on the uterus after cesarean section and the optimal algorithm for diagnostics. *Diagnostic radiology and radiotherapy*. 2019;(2):85-90. (In Russ.) DOI: 10.22328/2079-5343-2019-10-2-85-90
12. Setubal A, Alves J, Osório F, Guerra A, Fernandes R, et al. Treatment for Uterine Isthmocele, A Pouchlike Defect at the Site of a Cesarean Section Scar. *J Minim Invasive Gynecol.* 2018;25(1):38-46. DOI: 10.1016/j.jmig.2017.09.022
13. Nojinceva O.N., Bejenar V.F. The isthmocele of the scar on the uterus after the caesarean section is a new problem of a woman's reproductive health. *Journal of Obstetrics and Women's Diseases*. 2020;69(1):53-62. DOI: 10.17816/JOWD69153-62.

Information about the authors

Marina V. Galustyan, graduate student of the Department of Obstetrics, Gynecology and Perinatology at the Kuban State Medical University, Krasnodar, Russia. ORCID: 0000-0002-0448-7923. E-mail: doctor.mar@mail.ru.

Куценко Ирина Игоревна, д.м.н., проф., заведующая кафедрой акушерства, гинекологии и перинатологии, Кубанский государственный медицинский университет, Краснодар, Россия. ORCID: 0000-0003-0938-8286. E-mail: bio2302@mail.ru.

Боровиков Игорь Олегович, д.м.н., доцент, доцент кафедры акушерства, гинекологии и перинатологии, Кубанский государственный медицинский университет, Краснодар, Россия. ORCID: 0000-0001-8576-1359. E-mail: bio2302@mail.ru.

Магай Антон Сергеевич, аспирант кафедры акушерства, гинекологии и перинатологии, Кубанский государственный медицинский университет, Краснодар. Россия. ORCID: 0000-0003-2910-8798. E-mail: anton. magai@mail.ru.

Вклад авторов

М.В. Галустян — разработка дизайна исследования, получение и анализ данных, обзор публикаций по теме статьи, написание текста рукописи;

И.О. Боровиков — разработка дизайна исследования, обзор публикаций по теме статьи, написание текста рукописи;

И.И. Куценко — окончательное утверждение версии для публикации;

А.С. Магай — получение и анализ данных.

Получено / Received: 27.01.2021
Принято к печати / Accepted: 01.02.2021

Irina I. Kutsenko, Dr. Sci. (Med.), Prof., Head of the Department of Obstetrics, Gynecology and Perinatology of the Kuban State Medical University. Krasnodar, Russia. ORCID: 0000-0003-0938-8286 E-mail: bio2302@mail.ru.

Igor O. Borovikov, Dr. Sci. (Med.), As. Prof. of the Department of Obstetrics, Gynecology and Perinatology of the Kuban State Medical University. Krasnodar, Russia. ORCID: 0000-0001-8576-1359. E-mail: bio2302@mail.ru.

Anton S. Magay, graduate student of the Department of Obstetrics, Gynecology and Perinatology at the Kuban State Medical University, Krasnodar, Russia. ORCID: 0000-0003-2910-8798. E-mail: anton. magai@mail.ru.

Authors contribution

Marina V. Galustyan — research design development, obtaining and analysis of the data, review of publications on the topic of the article, writing the text of the manuscript;

Igor O. Borovikov — research design development, obtaining and analysis of the data, review of publications on the topic of the article, writing the text of the manuscript;

Irina I. Kutsenko — final approval of the version for the manuscript;

Anton S. Magay — obtaining and analysis of the data.

УДК: 618.393-079.5
DOI 10.21886/2219-8075-2021-12-1-62-67

Morphological verification of the first missed abortion

E.Y. Lebedenko[1], A.P. Milovanov[2], N.V. Sablina[3], T.V. Fokina[2], O.V. Gaida[1]

[1]Rostov State Medical University, Rostov-on-Don, Russia
[2]Research Institute of Human Morphology, Moscow, Russia
[3]S.P. Botkin City Clinical Hospital, Moscow, Russia

Objective. The study aimed to compare the level of INF α2 immunoexpression in tissues obtained during medical abortion with the corresponding level of IFNα2 expression in a retained fetal egg tissues after the first missed abortion. The authors compared the anamnestic data on previous inflammatory diseases of the genital tract with the results of an extended morphological study of the material obtained during the evacuation of the contents of the uterine cavity during the first non-developing pregnancy in the first trimester. **Materials and methods.** The study included 15 patients with first-time missed abortions caused by a viral infection (6-8 weeks of pregnancy). All patients demonstrated either recurrent herpes simplex labialis/genitalis or PCR confirmed HSV, HPV, CMV. Exclusion criteria were recurrent miscarriage, blighted ovum, endocrinopathies, male factor infertility, and other causes of miscarriage. The comparison group included 20 women of the same age that chose to undergo a medical abortion. **Results.** In patients from the comparison group, the main producer of IFN α2 was syncytiotrophoblast as well as maternal decidual cells in the parietal endometrium and uteroplacental area. In the main group, manifested hematogenous infection (microabscesses, vasculitis, lymphocytic and macrophage infiltration) with dystrophy and necrosis of decidual maternal cells and secondary pathological changes in the placental villi were diagnosed, which led to a significant decrease in the IFN α2 immunoexpression in all the studied cells. **Conclusion.** The lack of anamnestic data on previous urogenital infections does not exclude the etiological role of the inflammatory component in the genesis of non-developing pregnancy. First-time occurred pregnancy loss requires adequate postoperative interferon therapy and a thorough examination of a couple.

Keywords: first miscarriage, missed abortion, immunohistochemistry, IFN α2 deficiency, morphological study.

For citation: Lebedenko E.Y., Milovanov A.P., Sablina N.V., Fokina T.V., Gaida O.V. Morphological verification of the first missed abortion. *Medical Herald of the South of Russia.* 2021;12(1):62-67. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-62-67.

Corresponding author: Elena Yu. Lebedenko, lebedenko08@mail.ru.

Морфологическая верификация причин первой неразвивающейся беременности

Е.Ю. Лебеденко[1], А.П. Милованов[2], Н.В. Саблина[3], Т.В. Фокина[2], О.В. Гайда[1]

[1]Ростовский государственный медицинский университет, Ростов-на-Дону, Россия
[2]Научно-исследовательский институт морфологии человека», Москва, Россия
[3]Городская клиническая больница имени С.П. Боткина, Москва, Россия

Цель: сопоставить анамнестические данные о перенесенных воспалительных заболеваниях генитального тракта с результатами расширенного морфологического исследования вакуум-аспиратов полости матки при первой неразвивающейся беременности. **Материалы и методы**: I группа — 15 пациенток с первой неразвивающейся беременностью в сроках на 6–8-ой неделях гестации. У всех женщин отмечены эпизоды персистирующей вирусной инфекци: периодические герпетические высыпания на губах или половых органах, определение методом ПЦР в крови вируса простого герпеса (HSV), вируса папилломы человека (HPV) и цитомегаловируса (CMV). Исключены пациентки с привычным невынашиванием, анэмбрионией (по данным УЗИ), эндокринопатии, а также мужской фактор и другие причины ранней потери беременности. II группа — 20 здоровых женщин сопоставимого возраста, решившие прервать нежеланную беременность. Уровень иммуноэкспресии интерферона альфа-2 (IFN альфа 2) исследовали в клетках вакуум-аспиратов (синцитиотрофобласте ворсин и его депортантах, в децидуальных клетках париетального эндометрия и маточно-плацентарной области) по 3-хбалльной шкале. Расчет статистических данных выполняли на персональном компьютере с использованием программы «Microsoft excel 2011 для Mac» и статистической программы «Statistica». **Результаты**: в группе здоровых женщин основными продуцентами IFN альфа 2 стали синцитиотрофобласт ворсин и его депортанты, а также материнские децидуальные клетки в составе париетального эндометрия и маточно-плацентарной области. В основной группе диагностировано выраженное гематогенное инфицирование (микроабсцессы, васкулиты, лимфомакрофагальная инфильтрация) с дистрофией и некрозом децидуальных материнских клеток и вторичной патологией ворсин плацент, что привело к достоверному снижению иммуноэкспрессии IFN альфа 2 во всех изученных клетках. **Выводы**: отсутствие анамнестических данных о перенесённых урогенитальных инфекциях не исключает этиологическую роль воспалительного компонента в генезе неразвивающейся беременности. Первая

репродуктивная потеря требует адекватной интерферонотерапии после операции и тщательного обследования семейной пары для уточнения доказательных причин первой репродуктивной потери.

Ключевые слова: первая неразвивающаяся беременность, missed abortion, IFN α2 дефицит, морфологическое исследование.

Для цитирования: Лебеденко Е.Ю., Милованов А.П., Саблина Н.В., Фокина Т.В., Гайда О.В. Морфологическая верификация причин первой неразвивающейся беременности. *Медицинский вестник Юга России*. 2021;12(1):62-67. DOI 10.21886/2219-8075-2021-12-1-62-67.

Контактное лицо: Лебеденко Елизавета Юрьевна, lebedenko08@mail.ru.

Introduction

Non-developing pregnancy (NP) is a complication associated with the death of the embryo or fetus in the uterine cavity. The term «undeveloped pregnancy» used in Russian-speaking practice has been replaced in English-speaking countries by the definition of «miscarriage» (*missed abortion*), which more accurately reflects the nature of this pathology as no pregnancy progression when the embryo (fetus) is retained in the uterine cavity.

In modern obstetrics and gynecology, the generally accepted causes of reproductive losses on the mother's side are structural uterus disease, antiphospholipid syndrome, hormonal and metabolic disorders. Genetic disorders provoke 50–60% of reproductive losses early in gestation [1]. The role of mothers' medical conditions as to the termination of pregnancies mainly increases in the second and third trimesters of pregnancy. In 26–40% of cases, the causes of miscarriage are considered unknown.

It should be noted that the established concept of the significant role of chromosomal abnormalities as the main cause of gestational losses in the first trimester of pregnancy has formed a passive position among clinicians, which even in the absence of chromosomal abnormalities in fetal cells does not induce clinicians to verify other reproductive failure causes. As a result, the couple's desire to realize their reproductive function in the near term after their first loss early in gestation, associated with obstetricians' lack of a cautious attitude towards the first reproductive failure, translates the obstetric situation into habitual miscarriage.

The NP proportion in the structure of reproductive losses varies but remains at a fairly high level at 10–20%. According to Milovanov and Serova (2011), among the losses of the first trimester, NP was 4–10% of all confirmed pregnancies [2]. At the same time, 108 (60%) of 180 surveyed women with NP had inflammatory (most often viral) causes in the presence of subchronic forms or carriage of viruses. A combination of parietal and basal deciduitis, vasculitis, microabscesses, and other signs of viral cell damage was recorded in the abortive material.

Thus, when confirming NP, the most informative way of capturing the reasons is a detailed specification of anamnestic data and a detailed morphological study of the uterine cavity evacuated contents [3, 4].

The goal of the research was to compare the anamnestic data on previous inflammatory diseases of the genital tract with the results of an extended morphological study of vacuum aspirates of the uterine cavity during the first NP.

Material and methods

Group I included 15 nulliparous women (mean age, 29.4 ± 2.3 years) with the first NP at 6–8 weeks diagnosed by the progressive assessment of the blood β-hCG dynamics, as well as by ultrasound. The experimental group (II) included 20 healthy women of comparable age (27.1 ± 3.1 years) who wished to terminate an unplanned pregnancy by an artificial abortion at the same term.

The exclusion criteria were a history of childbirth, recurrent miscarriage, anembryonic pregnancy, as well as those associated with endocrinopathies and hemostasis disorders, surgical interventions on the uterus and cervix.

In both groups of patients, the emptying of the uterus was carried out at the gynecological department of the Public Funded Health Facility Municipal Clinical Hospital named after S.P. Botkin (Moscow) by vacuum aspiration (by the method regulated by Order No. 572n, as well as by the American College of Obstetricians and Gynecologists manual (2015) [5]), the Eschmann VP 35 apparatus (Great Britain) at an 80 kPa negative pressure or a plastic aspirator with a 60 ml volume using disposable plastic cannulas without prior dilation of the uterine cervix with intravenous anesthesia.

Infectious disease history, as well as the results of previous clinical and laboratory studies, was taken according to a specially developed questionnaire.

At the Research Institute of Human Morphology (Moscow), histologic sections were prepared from vacuum aspirates and stained with hematoxylin and eosin. After viewing in a Leica 2500 microscope (Germany), blocks with samples of placental villi, parietal endometrium, as well as the uteroplacental area, the junction of the villi with the uterine wall, were taken. Additional sections were cut from these blocks and, after dewaxing, were placed on polylysine-coated slides. Epitope retrieval was carried out in a microwave oven for 20 minutes in citrate buffer (pH 6.0). The following antibodies were used by immunoperoxidase technology: 1) IFNα2 polyclonal antibody of assessing the immunoexpression level: 1 point – light brown cytoplasm staining, 2 points – brown cytoplasm staining, 3 points –

dark brown cytoplasm staining; 2) rabbit monoclonal vimentin antibody (Vimentin EP21) for the determination of decidual stromal cells; 3) rabbit monoclonal granzyme B antibody (Granzyme B) – a marker of uterine natural killer cells. A detection system was used to visualize the immunoreaction results. Negative reactions to the reagents used were conducted.

The IFNα2 immunoexpression scoring was statistically processed by the Mann-Whitney U test.

Results

In the detailed study of the infectious history in Group I patients, it was established that four patients (26.7%) had acute inflammatory diseases of bacterial etiology only during this pregnancy diagnosed as non-developed. The rest (73.3%) had anamnestic data on acute viral diseases during pregnancy: acute herpesvirus and acute respiratory viral infection. Also, in these patients, herpes simplex virus-2 (HPV-2) – 40.0%, cytomegalovirus (CMV) – 26.6%, rubella virus – 26.6%, and bacterial agents – 26.6% were detected once in the blood before pregnancy by polymerase chain reaction. Seven patients (46.7%) had acute inflammatory diseases of viral and bacterial etiologies.

The histological processing of uterine vacuum aspirate in Group 1 patients showed that all patients had pronounced signs of hematogenous infection, in particular microabscesses, vasculitis, lymphoma-macrophage infiltration in the parietal endometrium, and uteroplacental area showing a pattern of acute or chronic endometritis. At the same time, markers of viral endometrial lesions were diagnosed in every second patient (50%). In 7 cases (46.7%), signs of basal deciduitis with microabscesses were visualized in the endometrium. Local bleeding disorders as arterial microthrombosis were detected in 11 cases (73.3%). At the same time, none of the patients included in the study had any blood coagulation disorders previously diagnosed. In 12 out of 15 cases (80%), rheological disorders were revealed according to the type of development of various age retrochorial hematoma.

Comparison of the anamnestic data on the transferred infectious and inflammatory diseases with the cytomorphological examination showed the following. In 11 (73.3%) patients, the cause of NP was local inflammation that arose by ascending or hematogenous infection, which, when the blastocyst was immersed in the endometrium and formed a chorionic sac, damaged glandular epithelial cells, decidual cells, and invade cytotrophoblast.

In four women (26.7%) who did not have an infectious history, morphological signs of inflammation associated with epithelial proliferation with cellular infiltration of the stroma were interpreted as a consequence of an inflammatory reaction resulting from the dead ovum retention in the uterine cavity and the chorionic villi rejection. In these patients, non-infectious factors were identified that caused the early fetal loss, having an allo-/autoimmune nature (abnormal activity of natural killer cells, the presence of alloimmune antibodies, human leukocyte antigen incompatibility between partners, thrombophilic conditions).

Histological processing of 20 vacuum aspirates from Group II patients showed no signs of an inflammatory reaction (decidual tissue, chorionic villi, progressive uterine pregnancy) which corresponded to the absence of anamnestic data on bacterial and viral infectious diseases before and during pregnancy.

Taking into account the data of some authors on the role of infectious agents as a trigger mechanism in the subsequent induction of autoimmune reactions of the endometrium [6], the development of secondary immunodeficiency and immunosuppressive states, it was of some interest to compare the levels of immunoexpression of interferon alpha-2 (IFNα2) in vacuum aspirate cells

Table 1 / Таблица 1

Scoring of IFNα2 immunoexpression in medical abortion (MA) and first occurred missed abortion caused by inflammation (NB) cells
Балльная оценка иммуноэкспрессии IFNα2 в клетках вакуум-аспиратов медицинских абортов (МА) и неразвивающейся беременности (НБ)

Исследуемые группы / *Study groups*	Выраженность иммуноэкспрессии IFNα2 в клетках (баллы) / *The severity of IFNα2 immunoexpression in cells (points)*			
	Синцитиотрофобласт ворсин / *Syncytiotrophoblast villi*	Депортанты / *Deportants*	Децидуальные клетки *Decidual cells*	
			Париетальный эндометрий / *Parietal endometrium*	Маточно-плацентарная область / *Uteroplacental region*
I группа / *1st group*	1,88 ±0,25*	2,06 ±0,24*	2,03 ±0,28*	1,85 ±0,20*
II группа/ *2nd group*	2,44±0,32	2,66 ±0,26	2,28 ±0,21	1,63 ±0,27

Note: ** — p <0.001 (Mann-Whitney comparison criterion).*
Примечание: * — p <0,001 (критерий сравнения Манна-Уитни).

after the first NP in terms of 6–8 weeks with the same in Group II (medical abortions).

The main object of the immunohistochemical study was cells producing IFNα2. In scoring, the immunoactivity of all cells producing IFNα2 in the patient group with NP (Group I) was significantly lower (Table 1).

Immunohistochemically, inflammatory infiltration was characterized by microabscesses in the uteroplacental area with the retention of IFNα2 producing cells only within the fibrinoid boundary layer (left) zone and death of decidual cells in the inflammatory zone (Figure 1). The approach of the villi near the chorionic sac wall and a decrease in the number of deportants were detected, a thinned syncytiotrophoblast was detected in the intervillous space with a reduced immunoexpression of IFNα2, and vasculogenesis was absent in the stroma (Figures 2 and 3).

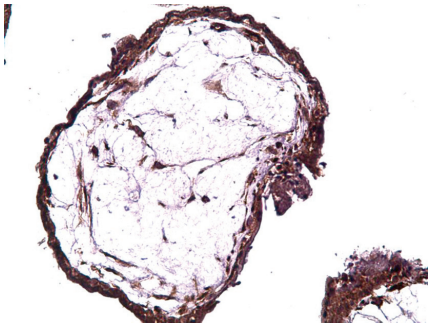

Figure 1. *Occurred missed abortion (7 weeks bp): microabscess in the uteroplacental region, retention of IFNa2-producing cells only in the zone of the fibrinoid boundary layer (left) and death of decidual cells in the inflammation zone, immunohistochemistry, x100.*

Рисунок 1. НБ (7 нед п.о.): микроабсцесс в маточноплацентарной области, сохранение IFNα2-продуцирующих клеток только в зоне пограничного слоя фибриноида (слева) и гибель децидуальных клеток в зоне воспаления, иммуногистохимия, х100.

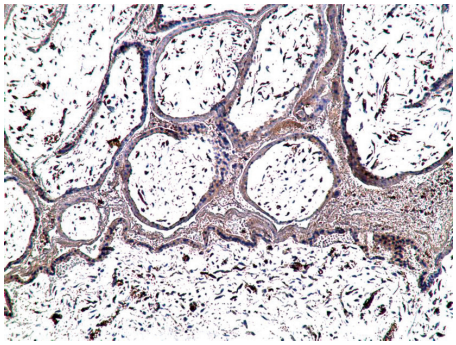

Figure 2. Occurred missed abortion (6 weeks): placental villi with thinned syncytiotrophoblast with reduced immunoexpression of IFN-2, in the stroma absence of vasculogenesis, x200.

Рисунок 2. НБ (6 нед): ворсина плаценты с истонченным синцитиотрофобластом при сниженной иммуноэкспресии IFNα2, в строме — отсутствие васкулогенеза, х200.

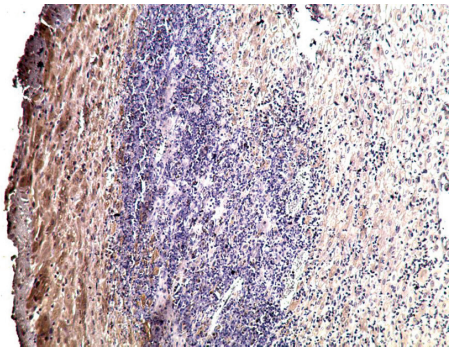

Figure 3. Occurred missed abortion (8 weeks): contiguous villi near the chorionic sac (bottom), lack of immunoexpression of IFN-2, in the stroma individual placental macrophages, x200.

Рисунок 3. НБ (8 нед): сближенные ворсины возле хориального мешка (внизу), отсутствие имууноэкспресии IFNα2, в строме — отдельные плацентарные макрофаги, х200.

In the immunohistochemical study of the cells in Group II patients, the maximum IFNα2 expression was found in the surface epithelium (syncytiotrophoblast) of the placental villi, as well as in its derivatives – deportants (Figure 4).

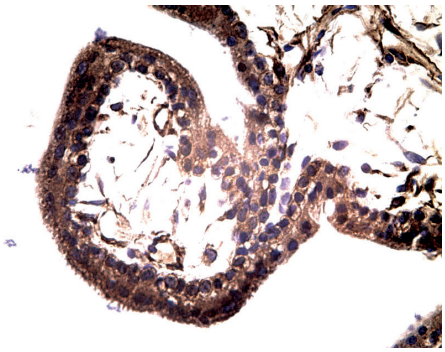

Figure 4. Artificial abortion — vacuum aspiration (6 weeks): placental villi with thick syncytiotrophoblast and pronounced expression of IFN-2, in the stroma intense vasculogenesis, immunohistochemistry, x 200.

Рисунок 4. Артифициальный аборт — вакуум-аспирация (6 нед): ворсины плаценты с толстым синцитиотрофобластом и выраженной экспрессией IFNα2, в строме — интенсивный васкулогенез, иммуногистохимия, х 200.

A pronounced immunoreaction (3 points) was visible in the syncytiotrophoblast cytoplasm and superficial brush border. Also, lateral epithelial diverticulum with many nuclei in the common cytoplasm became typical. The deportants and syncytiotrophoblast connections gradually diminished, and they ended up in the intervillous space, in the venous collectors.

The visualized placental villi were distinguished by thick syncytiotrophoblast and pronounced IFNα2 expression; intense vasculogenesis was found in the stroma (Figure 5).

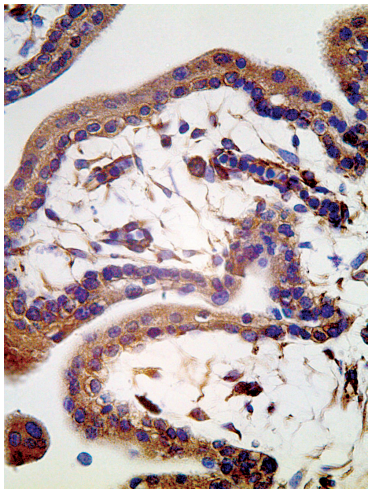

Figure 5. *Artificial abortion — vacuum aspiration (7 weeks): full-fledged villi near the chorionic sac, immunoexpression of IFNα2 in syncytiotrophoblast and stromal vessels (angiogenesis), immunohistochemistry, x 200.*

Рисунок 5. Артифициальный аборт — вакуум-аспирация (7 нед): полноценные ворсины возле хориального мешка, иммуноэкспрессия IFNα2 в синцитиотрофобласте и стромальных сосудах (ангиогенез), иммуногистохимия, х 200.

Discussion

A comparison of IFNα2 immunoexpression between patients after the first NP (Group I) and healthy women with a medical abortion (Group II) confirmed a significant deficiency of interferonogenesis in maternal decidual cells and placental structures such as syncytiotrophoblast and its deportants. During the physiological development of pregnancy in trimester I in Group II patients, significant IFNα2 production by syncytiotrophoblast of villi and its deportants with delivery to the maternal body, as well as maternal decidual cells in the parietal endometrium and uteroplacental region, was registered.

There is no doubt that this phenomenon is causally associated with a massive inflammatory process in the parietal endometrium and the uteroplacental area, as well as with the remote effect of local factors of maternal inflammation on the placental villi including the uterine killer cells' cytotoxic effect.

Conclusion

The data obtained correlate with the association of NP and chronic endometritis generally accepted at the FIGO 2006 International Congress [10]. However, the routine antibiotic prescription to each patient with NP without a proven causally significant infection must be recognized as irrational, since the use of chemotherapeutic agents for aseptic inflammation can enhance immunosuppression and aggravate structural and functional disorders of the endometrium.

The results obtained confirm the need to revise the stereotype formed among obstetricians-gynecologists to consider the first NP as a natural selection sporadic element. A reasonable approach to the subsequent recurrent miscarriage prevention among patients with a history of first NP should be the formation of a high-risk group of repeated reproductive failures. When confirming the virus-associated inflammatory cause of the first NP, it is necessary to carry out adequate interferon therapy in the postoperative period and a similar pregravid preparation for the next pregnancy.

Active identification of anamnestic data on persistent viral infection allows verifying its etiological role in the NP genesis, which consists in the development of endometrium morphofunctional changes with impaired normal cyclic transformation and tissue receptivity, impaired implantation, trophism, and early embryo loss. Unjustified antibiotic therapy with broad-spectrum drugs in the rehabilitation framework after NP leaves in the «shadow» the true etiological factors and mechanisms for stopping the pregnancy development. Comparison of infectious history data with a detailed morphological study clarifies the goals of subsequent preconception preparation when planning pregnancy, substantiates the feasibility and range of additional diagnostic measures for the prevention of repeated early reproductive losses.

Finansing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Адамян Л.В., Серов В.Н. *Выкидыш в ранние сроки беременности: диагностика и тактика ведения. Клинические рекомендации (протокол лечения).* – 2016.
2. Милованов А.П. Серова О.Ф. *Причины и дифференцированное лечение раннего невынашивания беременности.* - М. Студия МДВ; 2011.
3. *Ранние сроки беременности*. Под ред. В.Е. Радзинского, А.А. Оразмурадова. – М.; 2005.
4. Милованов А.П. *Патология системы мать-плацента-плод*.- М.: Медицина; 1999.
5. *Акушерство. Национальное руководство*. Под ред. Э.

REFERENCES

1. Adamyan L.V., Serov V. N. *Miscarriage in early pregnancy: diagnosis and management tactics. Clinical guidelines (treatment protocol).* 2016. (In Russ.)
2. Milovanov A.P. Serova O.F. *Causes and differential treatment of early miscarriage*. M. Studio MDV; 2011. (In Russ.).
3. Radzinsky V.E., Orazmuradov A.A., Eds. *Early pregnancy*. M; 2005. (In Russ.).
4. Milovanov A.P. *Pathology of the mother-placenta-fetus system.* M.: Medicine; 1999. (In Russ.)
5. Ailamazyan E. K., Kulakov V. I., Radzinsky V. E., Savelyeva G. M., eds. *Obstetrics. National leadership.* 2014. (In Russ.)

К. Айламазяна, В. И. Кулакова, В. Е. Радзинского, Г. М. Савельевой. - 2014.
6. Радзинский В.Е., Запертова Е.Ю., Мисник В.В. Генетические и иммунологические аспекты привычного невынашивания беременности. // *Акуш. и гин.* - 2005. - №6. – С.24-29. eLIBRARY ID: 9141156
7. Милованов А.П., Волощук И.Н. Депортированный синцитиотрофобласт и плацентарные микрочастицы в организме матери при нормальной беременности и преэклампсии (28 лет спустя). // *Архив патологии.* – 2017. - №79(1). - С: 61–7. DOI: 10.17116/patol201779161-67
8. Papadopoulos N, Simopoulos C, Karamanidis D, Kotini A, Tamiolakis D. Large granular lymphocytes activity in women with spontaneous abortions during the 1st trimester of gestation. .. *Panminerva Med.* - 2002. – V. 44(4). – P. 343-347.
9. Lambropoulou M. Tamiolokis N. Venizelos J., Liberis V., Galazios G., et al. Imbalance of mononuclear cell infiltrates in the placental tissue from after spontaneous abortion versus therapeutic termination from 8th to 12th weeks of gestational age. // *Clin. Exp. Med.* - 2006. – V. 6(4). – P.171- 176. DOI: 10.1007/s10238-006-0111-x.
10. *ACOG's Guide to Managing Miscarriage: Follow Patient Preference. Updated clinical management of early pregnancy loss focuses on patient choice.* Gupta S. Ed. - Medpageto- day, 04.22.2015.

6. RadzinskyV.E., Zapertova E.Yu., Misnik V.V. Genetic and immunological aspects of habitual miscarriage. *Akush. and gin.* 2005;6:24-29. (In Russ.). eLIBRARY ID: 9141156
7. Milovanov A.P., Voloshchuk I.N. Deported syncytiotrophoblast and placental microparticles in the mother's body during normal pregnancy and preeclampsia (28 years later). *Archive of pathology.* 2017;79(1): 1–6. (in Russ.). DOI: 10.17116/patol201779161-67
8. Papadopoulos N, Simopoulos C, Karamanidis D, Kotini A, Tamiolakis D. Large granular lymphocytes (LGLS) activity in women with spontaneous abortions during the 1st trimester of gestation. *Panminerva Med*. 2002;44(4):343-7. PMID: 12434116.
9. Lambropoulou M, Tamiolakis D, Venizelos J, Liberis V, Galazios G, et al. Imbalance of mononuclear cell infiltrates in the placental tissue from foetuses after spontaneous abortion versus therapeutic termination from 8th to 12th weeks of gestational age. *Clin Exp Med.* 2006;6(4):171-6. DOI: 10.1007/s10238-006-0111-x
10. Gupta S., ed. *ACOG's Guide to Managing Miscarriage: Follow Patient Preference. Updated clinical management of early pregnancy loss focuses on patient choice*. Medpageto- day, 04.22.2015.

Информация об авторах

Лебеденко Елизавета Юрьевна, д.м.н, доц., профессор кафедры акушерства и гинекологии №3, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0003-2602-1486. E-mail: lebedenko08@mail.ru.

Милованов Андрей Петрович, д.м.н., проф., главный научный сотрудник лаборатории патологии репродукции НИИ морфологии человека, Москва, Россия. ORCID: 0000-0001-8804-0258. E-mail: a_p_milovanov@mail.ru.

Саблина Наталья Валерьевна, врач акушер-гинеколог гинекологического отделения ГБУ здравоохранения г. Москвы «Городская клиническая больница им. С.П. Боткина» Департамента здравоохранения г. Москвы, Москва, Россия. ORCID:0000-0002-8068-120X. E-mail: natalie_sablina@yahoo.de.

Фокина Татьяна Васильевна, к.м.н., старший научный сотрудник лаборатории патологии репродукции НИИ морфологии человека, Москва, Россия, ORCID:0000-0002-2467-7660, тел: 8 (499) 129-2501.

Гайда Оксана Владимировна, доцент кафедры акушерства и гинекологии № 3, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-6966-1793. E-mail: gajdaoksana @mail.ru.

Information about the authors

Elizaveta Yu. Lebedenko, Dr.Sci. (Med.), associate professor, professor of the Department of obstetrics and gynecology №3, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0003-2602-1486. E-mail: lebedenko08@mail.ru.

Andrey P. Milovanov, Dr. Sci. (Med.), Head Researcher Reproduction Pathology Laboratory, Research Institute of Human Morphology. ORCID: 0000-0001-8804-0258. E-mail: a_p_milovanov@mail.ru.

Natalya V. Sablina, obstetrician-gynecologist, gynecologic department, S.P. Botkin City Clinical Hospital, Moscow, Russia. ORCID: 0000-0002-8068-120X. E-mail: natalie_sablina@yahoo.de

Tatyna V. Fokina, Cand. Sci. (Med.), Senior Researcher Reproduction Pathology Laboratory, Research Institute of Human Morphology. ORCID: 0000-0002-2467-7660.

Gaida Oksana Vladimirovna, Cand. Sci. (Med.), associate professor of the Department of Obstetrics and Gynecology, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-6966-1793. E-mail: gajdaoksana@mail.ru.

Вклад авторов

Вклад авторов в написании работы равнозначный.

Authors contribution

The contribution of the authors in writing the work is equivalent.

Получено / Recived: 01.02.2021
Принято к печати / Accepted: 09.02.2021

УДК: 612.017.1:616-092.9:547.995.15
DOI 10.21886/2219-8075-2021-12-1-68-73

Discoordination of the processes of activation and suppression of immunocompetent cells during mesotherapy with hyaluronic acid

L.P. Sizyakina, A.I. Sergeeva, I.I. Andreeva

Rostov State Medical University, Rostov-on-Don, Russia

Objective. The study aimed to assess the dynamics of the systemic immune response in patients during mesotherapy with hyaluronic acid (HA). **Materials and methods.** The observation group included 26 women who received the first-time mesocorrection with drugs based on hyaluronic acid (HA). Injections of low molecular weight HA were carried out according to standard methods in a course of 5 procedures with an interval of 14 days. The parameters of the innate and adaptive immune response were studied before and two weeks after the end of the course. The skin condition was assessed by dermatoscopy (Aramo Smart Lite 300, Southern Korea). **Results.** The clinical effect of the course of procedures was reflected in the subjective improvement in the appearance. The improvement was confirmed by hardware analysis, which recorded an increase in hydration, a smoothing of the skin relief, and a decrease in the depth of wrinkles. At the end of the course, redistribution of lymphocyte populations towards natural killer cells and B-lymphocytes was revealed with a decrease in the total number of T cells. The antibody production of immunoglobulins of classes M and G was increased, the serum content of Ig A and IgE was reduced, the number of both T-effectors and T-lymphocytes with immunosuppressive activity increased. Changes in the neutrophil system were characterized by the inhibition of the production of reactive oxygen intermediates; the dynamics of the expression of Toll-like receptors by monocytes was ambiguous. **Conclusion.** The results of the study confirmed the active involvement of the factors of innate and adaptive systemic response in the cosmetic effect, which manifested itself immediately after mesotherapy as systemic dysregulatory immune changes.

Keywords: hyaluronic acid, innate and adaptive immune response, mesotherapy.

For citation: Sizyakina L.P., Sergeeva A.I., Andreeva I.I. Discoordination of the processes of activation and suppression of immunocompetent cells during mesotherapy with hyaluronic acid. *Medical Herald of the South of Russia.* 2021;12(1):68-73. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-68-73.

Corresponding author: Irina I. Andreeva, iai3012@rambler.ru.

Дискоординация процессов активации и супрессии иммунокомпетентных клеток при мезотерапии гиалуроновой кислотой

Л.П. Сизякина, А.И. Сергеева, И.И. Андреева

Ростовский государственный медицинский университет, Ростов-на-Дону, Россия

Цель: оценить динамику системного иммунного реагирования пациентов при мезотерапии гиалуроновой кислотой (ГК). **Материалы и методы:** группу наблюдения составили 26 женщин, впервые выполняющих мезокоррекцию препаратами на основе гиалуроновой кислоты (ГК). Инъекции низкомолекулярной ГК проводились по стандартным методикам курсом 5 процедур с интервалом в 14 дней. До начала проведения и через две недели по окончании курса были исследованы параметры врождённого и адаптивного иммунного ответа. Состояния кожи оценивали методом дерматоскопии с использованием аппарата Aramo Smart Lite 300. **Результаты:** клинический эффект курса процедур отразился в субъективном улучшении внешнего вида и подтвержден аппаратным анализом, зафиксировавшем повышение увлажненности, выравнивание рельефа и уменьшение глубины морщин. По окончании курса процедур по сравнению с исходными данными выявлено перераспределение популяций лимфоцитов в сторону натуральных киллеров и В-лимфоцитов при снижении общего числа Т-клеток. При этом усилена антителопродукция иммуноглобулинов классов М и G и снижено сывороточное содержания Ig A и IgE, увеличено количество как Т-эффекторов, так и Т-лимфоцитов с иммуносупрессивной активностью. Изменения в системе нейтрофилов характеризуются угнетением продукции активных форм кислорода, а динамика экспрессии Toll-подобных рецепторов клетками моноцитарного ряда неоднозначна. **Заключение:** результаты исследования подтверждают активное вовлечение в реализуемый косметический эффект факторов врождённого и адаптивного системного ответа, что сразу по окончании процедур мезотерапии ГК проявляется в системных дисрегуляторных иммунных изменениях.

Ключевые слова: гиалуроновая кислота, врожденный и адаптивный иммунный ответ, мезотерапия.

Для цитирования: Сизякина Л.П., Сергеева А.И., Андреева И.И. Дискоординация процессов активации и супрессии иммунокомпетентных клеток при мезотерапии гиалуроновой кислотой. *Медицинский вестник Юга России.* 2021;12(1):68-73. DOI 10.21886/2219-8075-2021-12-1-68-73.

Контактное лицо: Ирина Ивановна Андреева, iai3012@rambler.ru.

Introduction

Presently, esthetic medicine develops intensively. It aims to correct the appearance of a person with medical methods [1, 2]. A specific peculiarity of this type of medicine is not only the diversity of methods and technologies applied but also the fact that their practical application significantly advances the theoretical justification of the mechanism of action. In this aspect, one of the leading positions (from the point of view of vast practical application) is occupied by mesotherapy with hyaluronic acid (HA) [3, 4]. The technology is based on the disturbance of the skin by injections of HA that exerts expressed immune tropic effect and involves the immune system to have an effect. The ambivalence of HA effects is well-known. Its highly molecular variant exerts anti-inflammatory, wound-healing, and immune-suppressive effects, while its low molecular fragments exert stimulating effects due to the impact on pattern recognizing receptors, which leads to the activation of signaling pathways of the synthesis of anti-inflammatory mediators [5]. The available modern publications on this subject are not consistent and, as a rule, they are dedicated to the characteristics of single factors of the immune response, do not contain the multicomponent analysis, and interaction of the reactions of the congenital and adaptive immunity of patients. These facts provide the rationale for the present study.

The study aimed to assess the dynamics of the systemic immune response in patients during mesotherapy with HA.

Materials and Methods

The group of observation included 26 women aged 45±10 years old) that underwent mesocorrection with HA-based drugs for the first time. The criteria of exclusion included previous mesotherapy, hormonal replacement therapy, combined oral contraceptives, acute infectious pathology, comorbid somatic pathology at the stage of subcompensation or decompensation, pregnancy, and lactation. The clinical study complied with "The guidelines for clinical practice in the Russian Federation" approved by the Decree of the Ministry of the Russian Federation dated June 19, 2003 No. 266. All patients signed informed consent for participation in the study. The study was approved by the local ethical committee of the Rostov State Medical University (protocol No. 19/19 dated October 3, 2019). The injection of low molecular HA was made by a standard method in a course of 5 procedures with a 14-day interval. Before the procedures and two weeks after the course, the parameters of the inborn and adaptive immunity were studied that included the evaluation of the expression of CD3, CD4, CD8, CD16, CD19, and CD25 by lymphocytes, intracellular levels of Foxp3, expression of TLR2, TLR4, and TLR9 on monocytes in the peripheral blood. The oxygen-dependent metabolic activity of neutrophils was evaluated by the nitroblue tetrazolium (NBT) test. The content of serum immunoglobulins A, M, and G was estimated by the reaction of radial immune diffusion in the gel according to the Manchini method, the level of IgE – by enzyme-linked immunosorbent assay. The evaluation of the skin condition (moisture content, the depth of folds and wrinkles) was performed using an apparatus Aramo Smart Lite 300. The study was carried out at the facilities of Ekaterininskaya Clinics, LLC and Chain of European Laboratories, LLC. Statistical analysis was conducted in the software R (version 3.2, R Foundation for Statistical Computing, Vienna, Austria). The results were presented as a central tendency for the median and interquartile range (25 and 75 percentile), in the text presented as Me [LQ; UQ]. The group medians were compared using Wilcoxon's test for linked samples. The differences were statistically significant at $p < 0.05$.

Results

The objective reflection of the subjective perception of the course of mesotherapy with HA was the analysis of the results of dermatoscopy using Aramo Smart Lite 300. The comparison of such parameters as moisture content and skin relief, evaluated before the procedures and two weeks after the therapy, showed an increase in the parameters of moisture content from 53% to 87% and a decrease in the relief of the skin folds and wrinkles from 74% to 45%. The changes in the immune response of patients were observed at the level of leukopoiesis as a statistically significant decrease in the total number of leukocytes (before injections – 6.65×10^9/L [5.2;7.9]; after injections – 6.25×10^9/L [5.2;7.4], $p = 0.003$) and an increase in the relative number of lymphocytes (before injections –32.5% [27;35], after injections – 36.5% [30;42], $p = 0.005$). The analysis of the parameters that characterize the functioning of the factors of inborn immunity showed that in comparison with the data obtained before the procedures, the changes after a

course of mesotherapy were observed in all the parameters. In particular, an increase in the peripheral circulation of the number of natural killers was registered. This fact was confirmed by not only relative but also absolute values: $CD16^+$ % before the therapy 11 [10;12], after the therapy – 12 [11;15], p = 0.004; $CD16^+$, 10^9/L before the therapy 0.25 [0.17;0.28], after the therapy – 0.27 [0.22;0.34], p = 0.002. The functional potential of neutrophils in the peripheral circulation decreased, indicating a decrease in the oxygen-producing activity, which was confirmed by the results of the NBT test. It was most evident in the case with a stimulated variant (NBT stim., CU 13 [11;7] and 11 [8;8], p=0.0003), while spontaneous production of active forms of oxygen changed less significantly (NBT spontaneous before the procedures – 9.5 [7;10], after – 8.0 [7;9], p = 0.035). The ambiguous effect of a course of mesotherapy with HA affected the expression of different variants of Toll-like receptor cells of monocyte series. Thus, for TLR 2 and TLR 9, an increase in the number of monocytes in the peripheral blood that carried these structures was revealed in relative and absolute variants of the evaluation: $CD14^+282^+$,% 3.31 [2.44;4.72] and 3.92 [2.73;4.54], p = 0.016; $CD14^+282^+$,10^9/L 0.061 [0.045;0.11] and 0.069 [0.048; 0.11], p = 0.008; CD 14^+289^+,% 3.35 [2.8;5.6] and 3.9 [3.1;5.2], p = 0.003; CD 14^+289^+,10^9/L 0.074 [0.06;0.11] and 0.091[0.067;0.12], p = 0.004. At the same time, on the contrary, the capacity of pattern recognition via TLR 4 decreased, which indicated a decrease in the relative number of TLR 4^+-monocytes ($CD14^+284^+$,% 3.7 [2.2;5.1] and 3.15 [2.05;4.7], p = 0.016). The absolute values did not have statistically significant differences.

The dynamic in the changes of quantitative and functional parameters of the adaptive immunity after a course of mesotherapy with HA in comparison with the data obtained before manipulations was observed for both cellular and humoral components. Thus, there was a decrease in the relative number of mature T-lymphocytes ($CD3^+$,% 69 [62;71] and 64.5 [57;70], p < 0.0001). However, the changes in the differentiation of the lymphoid lineage did not show significant changes in the absolute number of the peripheral T-lymphocytes ($CD3^+$,10^9/L 1.39 [1.11;1.66] and 1.38[1.12;1.6], p=0.9). The same peculiarity was observed also in the T-helper subpopulation: a statistically significant decrease in the relative number of total $CD4^+$-lymphocytes (37 [35;41]% to 34 [32;37]% after the therapy, p = 0.0004) and a lack of significant changes in the circulating pool of immune-competent cells ($CD4^+$,10^9/L 0.76 [0.66;0.93] and 0.74 [0.62;0.91], p = 0.65). It should be noted that there was a significant increase in the relative and absolute number of T-lymphocytes that formed the $CD8^+$-subpopulation and provided the realization of the cytotoxic effects of the cellular link of the adaptive protection: $CD8^+$,% 32 [29;35] and 34 [32;37], p = 0.0001; $CD8^+$,10^9/L 0.63 [0.53;0.84] and 0.74 [0.57;0.89], p = 0.004. Apart from the mentioned quantitative changes, there were dynamics observed in the functional parameters of T-cells of the immune response, in particular, an increase in the relative ($CD3^+CD25^+$,% 6 [5;7] and 7 [7;8], p = 0.002) and absolute values ($CD3^+CD25^+$,10^9/L 0.13 [0.097;0.16] and 0.15 [0.12;0.19], p = 0.001) of the number of T-lymphocytes that express CD25, a receptor responsible for the activation of the intracellular signaling pathways mediated by a universal immune-stimulating IL-2. Another functional parameter associated with the regulation of the activation potential of the immune response showed dynamic changes during mesotherapy of HA. An increase in the fixed number of the relative number of peripheral T-regulatory lymphocytes with the phenotype $CD4^+CD25^+Foxp3^+$ that are also responsible for immune suppression (4.75[4.1;6.1] and 4.9[4.3;6.7], p = 0.038) was observed. However, in absolute values, the observed dynamics were not statistically confirmed, although there was a certain tendency ($CD4^+CD25^+Foxp3^+$,10^9/L 0.11 [0.071;0.12] and 0.11 [0.085; 0.14], p = 0.11). In the humoral link of the adaptive immunity, an increase in the circulative pool of immune-competent cells was observed in the relative ($CD19^+$,% 22.5 [22; 24] and 25 [23; 26], p < 0.0001) and absolute (CD19+,10^9/L 0.49 [0.4; 0.57] and 0.52 [0.42; 0.65], p = 0.001) content in the number of B-lymphocytes. One should note not only the enhancement of the differentiation shift to precursors of anti-body production but also the activation of the synthesis of immunoglobulins M (IgM, g\L to 1.38 [1.13; 2.11], after the therapy – 2.13 [1.31; 2.76], p = 0.004) and G (IgG 15.4 [13.5; 18] and 17.1 [13.7; 19], p = 0.007). There was a statistically significant decrease in the serum levels IgA (IgA, g/L to – 2.42 [1.2;3.2], after the therapy – 1.39 [0.99;2.7], p = 0.0002) and IgE (IgE, IU/ml 12.8 [7;30] and 9[6;20], p = 0.0009). It should be mentioned that there was a statistically significant increase in the content of circulating immune complexes (CIC, CU. 11.9 [10.8;16] and 12.9 [11.1;18.8], p = 0.019).

Discussion

Mesotherapy is a course intradermal injection of different drugs. In the present study, low molecular HA was used for cosmetic effect due to the improvement of the skin properties at the site of injection. The obtained results showed that all the participants reached the desirable results. This was not only a subjective perception of the appearance improvement but was also proved instrumentally by the results of dermatoscopy, which showed an increase in the moisture level, smoothening of the relief, and a decrease in the depth of wrinkles. It can be suggested that the immune system of the skin is involved in the realization of the obtained effect due to the immune trophic properties of HA. Since skin-associated lymphoid tissue is one of the

components of multilevel functioning of the system of the immune response, the changes registered during the study of the properties of the immune-competent cells of the peripheral circulation reflect the effects of mesotherapy with HA. The obtained data confirmed the active involvement of the factors of inborn and adaptive systemic responses. Thus, two weeks after the end of the course, redistribution of differentiation inside lymphoid lineage to the side of natural killers and B-lymphocytes was observed. At the same time, antibody production of immunoglobulins M and G was enhanced. A certain decrease in the serum content of IgA can be explained by the activation of the local mucosal immune response. A decrease in the production of IgE can be associated with an enhancement of cytokine regulation of Th1 immune reactions. The latter suggestion was confirmed by the changes inside the T-cells population of lymphocytes, wherein the number of T-effectors was increased, and the differentiation of the natural killers. It should be highlighted that the data were obtained that confirmed the association of two oppositely directed reactions of immune regulation: enhancement of the processes of activation of T-lymphocytes and a shift of differentiation of T-helpers to $CD4^+CD25^+Foxp3^+$-lymphocytes with immune suppressive activity. It should be mentioned that the parameters of the inborn immunity at the systemic level were characterized by both an increase and a decrease in the functional potency. Along with the activation of natural killers, in the system of neutrophils, a suppression of oxygen-producing activity was registered, and the changes in the monocyte cells were ambiguous: an increase in the expression of TLR 2 and TLR 9 was associated with a tendency to a decrease in the number of $TLR4^+$-monocytes (Figure 1).

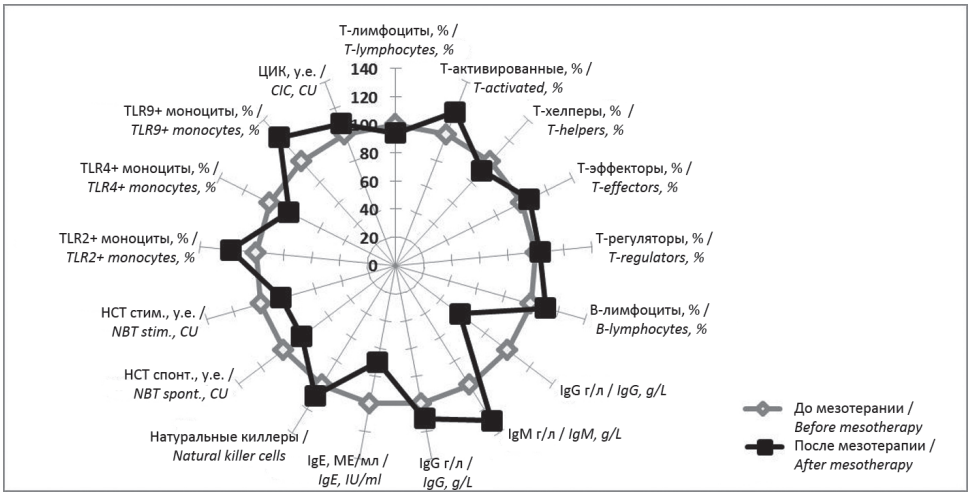

Figure 1. Changes in the parameters of the functioning of the immune system of patients after a course of mesotherapy with hyaluronic acid. Data before mesotherapy are taken as 100%.

Рисунок 1. Изменения параметров функционирования иммунной системы пациентов после курса мезотерапии гиалуроновой кислотой. Данные до мезотерапии приняты за 100%.

It should be mentioned that the obtained data agree with the results obtained by other authors that indicated a consecutive involvement of pro-inflammatory [6] and anti-inflammatory [7] cytokines in response to HA, an important role of Treg [8–10] in the recreation and maintenance of collagen, and involvement of Toll-like receptors in the initiation of immune tropic effects of HA [11, 12]. The presented publications are dedicated to the characteristics of single parameters, while the obtained data confirm the association of all the mentioned factors.

Conclusion

The results of the study reflect the dynamics of the systemic immune changes right after the end of the course of mesotherapy with HA. Further observation after the development of these patients allowed defining the period of resolution of the appeared dysregulatory changes and establishing the character and degree of the expression of these changes with the duration and quality of the clinical effect.

Financing. *The study did not have sponsorship (mandatory section).*

Источник финансирования. Исследование не имело спонсорской поддержки

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Караулов А. В., Юцковский А. Д. *Клиническая иммунология в дерматовенерологии и косметологии*.– Владивосток: Медицина ДВ; 2013.
2. Ходаченко В.В., Сизякина Л.П., Сидоренко О.А. Эффекты ботулинического токсина А при инволюционных изменениях кожи (клинико-иммунологическое исследование). // *Цитокины и воспаление*. – 2014.– Т.13, № 3. – С.140-142. eLIBRARY ID: 22840563
3. Щёткина М. В. История возникновения инъекционного метода введения препаратов мезотерапии. Современная актуальность процедуры. // *Здравоохранение Дальнего Востока*. – 2019.– № 3 – С. 87-90. DOI: 10.33454/1728-1261-2019-3-87-90
4. Калюжная Л.Д., Шармазан С.И., Моисеева Е.В., Бондаренко И.Н. Место гиалуроновой кислоты в проблеме старения кожи. // *Естетичная медицина*. – 2009. – Т4, № 10. – С. 44-46.
5. Михайлова Н. П., Базарный В. В., Кочурова И. В. Иммунотропные эффекты гиалуроновой кислоты в дерматологии. // *Мезотерапия*. – 2012. – Т 17, № 1. – С. 5-7.
6. Vistejnova L., Safrankova B., Nesporova K., Slavkovsky R., Hermannova M., et al. Low molecular weight hyaluronan mediated CD44 dependent induction of IL-6 and chemokines in human dermal fibroblasts potentiates innate immune response.// *Cytokine.*–2014 – Vol.70, №2. – P. 97-103. DOI: 10.1016/j.cyto.2014.07.006
7. Singampalli K.L., Balaji S., Wang X., Parikh U.M., Kaul A., et al. The Role of an IL-10/Hyaluronan Axis in Dermal Wound Healing. // *Front Cell Dev Biol*. –2020.– Vol.8. – Article 636. – P.1-15. doi: 10.3389/fcell.2020.00636.
8. Wang X., Balaji S., Steen E.H., Li H., Rae M.M., et al. T Lymphocytes Attenuate Dermal Scarring by Regulating Inflammation, Neovascularization, and Extracellular Matrix Remodeling. // *Adv Wound Care (New Rochelle).*– 2019.– Vol.8, №11. – P. 527-537. doi: 10.1089/wound.2019.0981
9. Zhang C., Li L., Feng K., Fan D., Xue W., Lu J. 'Repair' Treg Cells in Tissue Injury.// *Cell Physiol Biochem*. –2017.– Vol. 43, № 6– P. 2155-2169. doi: 10.1159/000484295.
10. Lam A.J., MacDonald K.N., Pesenacker A.M., Juvet S.C., Morishita K.A., et al. Innate Control of Tissue-Reparative Human Regulatory T Cells. // *J Immunol.* –2019.– Vol. 202, №8– P. 2195-2209. doi: 10.4049/jimmunol.1801330
11. Termeer C., Benedix F., Sleeman J., Fieber C., Voith U., et al. Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4. // *J Exp Med*. –2002.– Vol. 195, №1– P. 99-111. doi: 10.1084/jem.20001858.
12. Scheibner K.A., Lutz M.A., Boodoo S., Fenton M.J., Powell J.D., Horton M.R. Hyaluronan fragments act as an endogenousdanger signal by engaging TLR2. // *J Immunol*. –2006. – №177– P. 1272-1281. doi: 10.4049/jimmunol.177.2.1272.

Информация об авторах

Сизякина Людмила Петровна, д.м.н., проф., заведующий кафедрой клинической иммунологии и аллергологии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0001-5716-4397. E-mail: msiziakina@mail.ru.

Сергеева Александра Игоревна, аспирант кафедры клинической иммунологии и аллергологии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-8897-2386. E-mail: Aleksandra.sergeeva.87@mail.ru.

REFERENCES

1. Karaulov A. V., Yutskovsky A. D. *Clinical immunology in dermatovenerology and cosmetology*. Vladivostok: Medicine of the Far East; 2013. (In Russ.).
2. Khodachenko V.V., Sizyakina L.P., Sidorenko O.A. The effects of botulinum toxin A in involutional skin changes (clinical and immunological study). *Cytokines and inflammation*. 2014;13(3):140-142. (In Russ.). eLIBRARY ID: 22840563
3. Shchetkina M.V. The history of the emergence of the injection method of introducing mesotherapy drugs. Modern actuality of the procedure. *Healthcare of the Far East.* 2019;3:87-90. (In Russ.). DOI: 10.33454/1728-1261-2019-3-87-90
4. Kalyuzhnaya L.D., Sharmazan S.I., Moiseeva E.V., Bondarenko I.N. The place of hyaluronic acid in the problem of skin aging. *Aesthetic medicine*. 2009;4(10):44-46. (In Russ.).
5. Mikhailova N.P., Bazarny V.V., Kochurova I.V. Immunotropic effects of hyaluronic acid in dermatology. *Mesotherapy.* 2012;17(1):5-7. (In Russ.).
6. Vistejnova L, Safrankova B, Nesporova K, Slavkovsky R, Hermannova M, et al. Low molecular weight hyaluronan mediated CD44 dependent induction of IL-6 and chemokines in human dermal fibroblasts potentiates innate immune response. *Cytokine.* 2014;70(2):97-103. DOI: 10.1016/j.cyto.2014.07.006
7. Singampalli KL, Balaji S, Wang X, Parikh UM, Kaul A, et al. The Role of an IL-10/Hyaluronan Axis in Dermal Wound Healing. *Front Cell Dev Biol*. 2020;8:636. doi: 10.3389/fcell.2020.00636.
8. Wang X, Balaji S, Steen EH, Li H, Rae MM, et al. T Lymphocytes Attenuate Dermal Scarring by Regulating Inflammation, Neovascularization, and Extracellular Matrix Remodeling. *Adv Wound Care (New Rochelle).* 2019;8(11):527-537. doi: 10.1089/wound.2019.0981
9. Zhang C, Li L, Feng K, Fan D, Xue W, Lu J. 'Repair' Treg Cells in Tissue Injury. *Cell Physiol Biochem.* 2017;43(6):2155-2169. doi: 10.1159/000484295.
10. Lam AJ, MacDonald KN, Pesenacker AM, Juvet SC, Morishita KA, et al. Innate Control of Tissue-Reparative Human Regulatory T Cells. *J Immunol.* 2019;202(8):2195-2209. doi: 10.4049/jimmunol.1801330.
11. Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, et al. Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med.* 2002;195(1):99-111. doi: 10.1084/jem.20001858.
12. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. *J Immunol.* 2006;177(2):1272-81. doi: 10.4049/jimmunol.177.2.1272.

Information about the authors

Lyudmila P. Sizyakina, Dr. Sci. (Med.), professor, head of the department of clinical immunology and allergology. Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0001-5716-4397. E-mail: msiziakina@mail.ru.

Alexandra I. Sergeeva, Postgraduate student of the department of clinical immunology and allergology, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-8897-2386. Email: Aleksandra.sergeeva.87@mail.ru.

Андреева Ирина Ивановна, д.м.н., профессор кафедры клинической иммунологии и аллергологии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-7735-4275. E-mail: iai3012@rambler.ru.

Irina I. Andreeva, Dr. Sci. (Med.), professor of the department of clinical immunology and allergology. Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-7735-4275. E-mail: iai3012@rambler.ru.

Вклад авторов:

Л.П. Сизякина — разработка дизайна исследования;
А.И. Сергеева — получение и анализ данных;
И.И. Андреева — написание текста рукописи.

Authors contribution:

L.P. Sizyakina — research design development;
A.I. Sergeeva — obtaining and analysis of the data;
I.I. Andreeva — writing the text of the manuscript.

Получено / Received: 17.11.2020
Принято к печати / Accepted: 15.12.2020

УДК: 616-073.96:379.835:572]-053.2
DOI 10.21886/2219-8075-2021-12-1-74-81

Morphological and functional criteria for the effectiveness of recreational activities in children

A.V. Tarakanov[1], E.V. Chaplygina[1], E.S. Elizarova[1], T.D. Tarakanova[1], O.V. Korshunov[2]

[1]Rostov State Medical University, Rostov-on-Don, Russia
[2]Children's sanatorium health camp "Mir"

Objective. The study aimed to perform a comprehensive morphofunctional assessment of the effectiveness of recreational activities in children aged 9–12 years in the summer of 2019. **Materials and methods.** The study was conducted by the "Problem scientific laboratory of physical methods of diagnosis and treatment" of RostGMU in the children's health and recreation camp "Mir" (Krasnyi Desant village, Gulf of Taganrog). Procedures and time of the study: somatometry, bioimpedance analysis, cardiointervalography, stabilometrics on the 2nd day of stay and 2.5 weeks after. Two groups were formed: Group I included overweight children (OW), n = 15 (boys, n = 9; girls, n = 6); Group II included children with normal physical development (NPD), n = 37 (boys, n = 17; girls, n = 20). The children received a non-drug complex of camp resource provision for 3 weeks. **Results.** Health measures did not lead to significant changes in the somatometric parameters. According to the results of the cardiointerval recording, an authentic increase in the variational range and vegetative rhythm index was found in children with NPD, which indicates an increase in the parasympathetic activity of regulation. The stress index decreased by 30% in the case of NPD, and by 6% in the case of OW. Data from the stabilometric "Balls" simulator showed that after the recovery, the regulation of postural control was optimized, and decision-making processes were accelerated, especially in children with NPD. **Conclusion.** The study showed that in order to assess the effectiveness of recreational activities, along with "mandatory" methods, it is advisable to use functional methods such as cardiointervalography and stabilometrics, which can be recommended for use in health and rehabilitation institutions to assess the adaptive capabilities of the organism.

Keyword: improving children's health, somatometry, bioimpedance analysis, cardiointervalography, stabilometry.

For citation: Tarakanov A.V., Chaplygina E.V., Elizarova E.S., Tarakanova T.D., Korshunov O.V. Morphological and functional criteria for the effectiveness of recreational activities in children. *Medical Herald of the South of Russia.* 2021;12(1):74-81. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-74-81.

Corresponding author: Alexander V. Tarakanov, dr-tarakanov@yandex.ru.

Морфологические и функциональные критерии эффективности оздоровительных мероприятий у детей

А.В. Тараканов[1], Е.В. Чаплыгина[1], Е.С. Елизарова[1], Т.Д. Тараканова[1], О.В. Коршунов[2]

[1]Ростовский государственный медицинский университет, Ростов-на-Дону, Россия
[2]Детский санаторный оздоровительный лагерь «Мир», Ростовская область, Россия

Цель: комплексная морфофункциональная оценка эффективности оздоровительных мероприятий у детей 9–12 лет в летний период 2019 г. Материалы и методы: исследование проводилось «Проблемной научной лаборатории физических методов диагностики и лечения» РостГМУ в детском санаторном оздоровительном лагере «Мир» (х. Красный Десант, Таганрогский Залив). Порядок и время исследования: соматометрия, биоимпедансометрия, кардиоинтервалография, стабилометрия на 2-е сутки пребывания и через 2,5 недели. Сформированы две группы: I группа — избыточная масса тела (ИзМТ), n = 15 (мальчики, n = 9); девочки, n = 6); II группа — нормальное физическое развитие (НФР), n = 37 (мальчики, n = 17; девочки, n = 20). В течение трёх недель дети получали немедикаментозный комплекс ресурсного обеспечения лагеря. Результаты: оздоровительные мероприятия не привели к значимым изменениям соматометрических показателей. По результатам КИГ установлено достоверное повышение вариационного размаха и вегетативного показателя ритма у детей с НФР, что свидетельствует о повышении парасимпатической активности регуляции. Индекс напряжения при НФР снижался на 30%, а с ИзМТ — на 6%. Данные стабилометрического тренажёра «Мячики» показали, что после оздоровления оптимизируется регуляция позного контроля, ускоряются процессы принятия решения, особенно у детей с НФР. Заключение: исследование показало, что для оценки эффективности оздоровительных мероприятий наряду с «обязательными» методами целесообразно использовать такие функциональные методы, как кардиоинтервалография и стабилометрия, которые могут быть рекомендованы к использованию в оздоровительных и реабилитационных учреждениях для оценки адаптационных возможностей организма.

Ключевые слова: оздоровление детей, соматометрия, биоимпедансометрия, кардиоинтервалография, стабилометрия.

Для цитирования: Тараканов А.В., Чаплыгина Е.В., Елизарова Е.С., Тараканова Т.Д., Коршунов О.В. Морфологические и функциональные критерии эффективности оздоровительных мероприятий у детей. *Медицинский вестник Юга России.* 2021;12(1):74-81. DOI 10.21886/2219-8075-2021-12-1-74-81.

Контактное лицо: Тараканов Александр Викторович, dr-tarakanov@yandex.ru.

An important indicator of children and adolescents' health status is their physical growth and development, which is traditionally characterized by the assessment of morphological features such as basic somatometric indicators (length and body weight), somatic type (body type), less often the component composition of body weight [1, 2]. However, for a developing organism, an equally important aspect is the study of the child's adaptive capabilities, as one of the health indices. Based on the theory of functional system concepts, it becomes possible not only to state the fact of health at a given time but also to answer the question by what mechanisms and at what cost of adaptation this state is achieved and maintained when the external and internal environment conditions change [3].

To compensate for mental and physical stress, physical inactivity, unbalanced nutrition, and computer «aggression», recreational activities are necessary for traditional summer holidays. The degree of recovery effectiveness, as a rule, consists of the dynamics of height, weight, muscle strength, and vital capacity[1],[2]. These are the so-called «obligate» indices for assessing health improvement effectiveness. However, practice shows that with short health improvement periods (2–3 weeks), there are minor changes in these indices, especially height and weight. Growth rates are also different in different periods of childhood. Health improvement indices should be compared in appropriate groups for age and gender, body mass index (BMI), and other indices.

In the authors' opinion, an important factor in assessing health improvement is an integrated approach based on morphological and functional criteria. The study of functional indices allows establishing positive shifts even without the dynamics of «obligate» indices. As an example, the task was set to comprehensively assess the health improvement of children in the prepubertal period of 9–12 years using anthropometry, bioimpedansometry, cardiointervalography, and stabilometry methods.

The selection criteria for these methods were the following. The advantages of bioimpedansometry are acceptable accuracy and high reproducibility of measurement results, the comfort of research, and the convenience of automatic data processing. The obtained indices correlate with those of other more laborious and most accurate research methods [4, 5]. The study of heart rate variability is an accessible and not difficult method for a child to assess the regulation mechanisms of physiological functions in the human body, in particular heart neurohumoral regulation, the sympathetic/parasympathetic part ratio of the autonomic nervous system [6]. The study of children's statokinetic indices by computer stabilometry in the adaptive restructuring process is a method that is relatively rarely used to assess the efficacy of health-improving measures. It shows changes in the brain regulatory functions and is also not burdensome, and the technique is simple [7, 8].

The goal of the research is a comprehensive assessment of the effectiveness of recreation activities in children aged 9–12 years in the summer by anthropometry, bioimpedansometry, cardiointervalography, and stabilometry.

Materials and methods

The research was carried out by the staff of the «Problem Scientific Laboratory of Diagnostic Physical Methods and Treatment» of the Rostov State Medical University based on children's sanatorium recreation camp «Mir» on the Taganrog Bay shore (Rostov Region, Krasny Desant farmstead). For 21 days, children received the entire non-drug complex of center resource support.

Fifty-two children (26 boys and 26 girls) aged 9–12 years were examined on the 2nd day and after 2.5 weeks of a health improvement course in the summer (August 2019, 4th session).

At the beginning and the end of health improvement, the studies were carried out as follows: somatometry, bioimpedansometry, cardiointervalography, and stabilometry. The entire study complex was carried out for 35–40 minutes.

Somatometry was carried out according to the method of Bunak [9] in the morning using standard instrumentation. The results obtained were evaluated according to centile tables recommended in practical health care for medical status monitoring of children's groups by age and gender group.

Anthropometric indices related to the «obligate» ones such as body weight, body length, followed by calculation

[1] Effectiveness assessment tool for health improvement in out-of-town stationary institutions for rest and recuperation for children: Guidelines. – Moscow: Federal Center for Hygiene and Epidemiology of Rospotrebnadzor; 2011.

[2] Effectiveness assessment tool for health improvement in stationary organizations for rest and recuperation for children. Guidelines. – Moscow: State sanitary and epidemic regulation of the Russian Federation; 2018.

of Quetelet's BMI, and the indices necessary for carrying out bioimpedansometry (chest circumference, waist circumference, hip circumference, thigh circumference, wrist circumference, belly fat fold) were measured.

According to the value of BMI, children were further divided into two groups: Group I – obese children (oBMI), n = 15 (boys – n = 9, age 10.3 ± 0.4 years); girls – n = 6, age 11.2 ± 0.5 years); Group II – children with normal somatic growth (NSG), n = 37 (boys – n = 17, age 9.9 ± 0.3 years; girls – n = 20, age 9.7 ± 0.2 years). There were no children deficient in body mass in this sample.

The indices of muscle strength (dynamometry), vital capacity [2, 3], blood pressure, and heart rate per 1 minute were measured.

Changes in body composition were assessed by bioimpedansometry using a Diamant-AIST a body composition analyzer (ZAO Diamant, St. Petersburg) complete with a computer and special software. The measurements were carried out according to the standard four-electrode scheme in the supine position of the child with the electrode location on the wrist and ankle joints. The researchers studied such indicators as BMI, absolute values of fat, fat-free, and active cell mass (FM, FFM, ACM in kg), relative values of fat, fat-free, and active cell mass (%FM, %FFM, %ACM), total water, total fluid volume, extracellular fluid volume, intracellular fluid volume, and basal metabolism.

The functional state of the autonomic nervous system was determined by variation pulsometry. An «ANKAR-131» cardioanalyzer with software (OOO Medicom MTD, Taganrog) was used. Recording time was 5 minutes with the recommended standard conditions for the procedure (in the first half of the day, 2 hours after eating, dark room, room temperature 23–26 °C, the absence of auditory and visual irritation with preliminary adaptation to recording in the supine position 8–10 minutes). Statistics, variation pulsometry, spectral analysis were studied.

Stabilometry was carried out using a Stabilan-01-2 stabilograph with biofeedback (ZAO OKB RITM, Taganrog). The complex has a significant range of assessment of the center-of-pressure coordinates (± 200 mm from the force plate center) which allows eliminating restrictions in the subject's feet setting and is convenient for children. The «Balls» simulator with a game component carried out on a force plate was used. In the test process, the child must with a cross showing the center of pressure position on the force plate plane grab the ball that appears in a random place on the black field of the game, and change the position of the body to place it in one of the three baskets highlighted in yellow. The basket can be in any of three randomly distributed positions. For each ball placed in the yellow basket, 2 points are awarded, and for a ball placed in another (gray) basket, the number of errors increases. The goal of the game is to score maximum points and make a minimum of mistakes [5]. Before the study, a preliminary test was carried out.

Statistical analysis of results. In the beginning, the samples were checked for normal distribution using the Shapiro-Wilk test. When the coefficient was $p \geq 0.05$, the null hypothesis was accepted, that is, the sample complied with the normal distribution law. The parametric Student's t-test was used to compare the indexes in the groups. In the absence of a normal distribution, the Mann-Whitney test was used. When comparing before and after recreation activities within one group, the samples were dependent, when comparing indexes between the first and the second groups, the sample was independent. Differences were considered statistically significant at $p \leq 0.05$. At $p > 0.05$, the differences were considered statistically insignificant.

Results

Anthropometry and bioimpedansometry in Groups I and II are presented in Table 1. The task of comparative performance analysis of children with oBMI and NSG in these studies was not the main one. However, the table shows that all of these parameters in both groups have a significant statistical difference. Thus, the average body weight of children with oBMI exceeds the weight of children with NSG by almost 37%, but at the same time, the growth of these children is 7% higher. A significant difference is an excessive adipose mass (31.4% versus 19.8%) in children with NSG. However, %ACM has significant differences between children with NSG (50.8%) and children with oBMI (45.2%).

The next criterion for assessing recreation activities was functional shifts in the heart autonomic regulation. Probably, an extended movement regimen, water procedures, sports competitions should have a more significant effect on the cardiointervalogram parameters. The research results are presented in Table 2.

Table 2 shows that the initial levels of heart rate regulation in children with oBMI and NSG also differ. This includes the data of the rhythmogram spectral analysis. The high frequency (HF) wave power reflecting the spectral power of respiratory waves and the parasympathetic cardio-inhibitory center activity of the medulla oblongata is significantly lower in children with oBMI. A decrease in parasympathetic tone and an increase in sympathetic tone in this category of children is confirmed by an increase in the vagosympathetic balance coefficient (LF/HF) and the relative value of the low-frequency wave (LF) power which also reflect the activity of the medulla oblongata sympathetic centers. The sympathetic tone activation in children with oBMI comes against the backdrop of an increase in the very low-frequency wave (VLF) power reflecting the activity of the central ergotropic and humoral-metabolic mechanisms of heart rate regulation.

The next stage in the health improvement assessment was a recovery simulator related to the stabilographic game based on the biofeedback principle. The test processing results are presented in Table 3. After health improvement in both groups, the number of points scored significantly

Table 1 / Таблица 1

Dynamics of anthropometry and bioimpedance metrics during summer health events (M±m)
Динамика показателей антропометрии и биоимпедансометрии при летних оздоровительных мероприятиях (M±m)

Показатели *Parameters*	I группа *I group*		II группа *II group*		p
	до / *before*	после / *after*	до / *before*	после / *after*	
	1	2	3	4	5
МТ, кг / *Body weight, kg*	53,8±2,1	52,4±2,1	33,8±0,9	33,5±0,9	$p_{12до}$=0,001* $p_{12после}$=0,001*
p до/после / *p before/after*	0,92		0,85		
ДТ, см / *Body length, cm*	152,4±2,2	152,7±2,2	142,4±1,4	142,8±1,4	$p_{12до}$=0,0003* $p_{12после}$=0,0004*
p до/после	0,8		0,8		
ИМТ, кг/м² / *Body mass index, kg/m²*	23,1±0,8	22,5±0,7	16,5±0,3	16,2±0,3	$p_{12до}$=0,0001* $p_{12после}$=0,0002*
p до/после	0,5		0,78		
ЖМ, кг / *Fat mass, kg*	16,1±1,7	16,3±1,2	6,8±0,4	6,5±0,4	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,64		0,53		
%ЖМ, % / *%Fat mass, %*	31,4±1,4	30,6±1,4	19,8±0,6	19,0±0,6	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,68		0,36		
БЖМ, кг / *Fat-free mass, kg*	36,7±1,2	36,4±1,3	26,9±0,6	27,1±0,6	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,86		0,84		
АКМ, кг / *Active cellular mass, kg*	24,2±0,7	24,1±0,8	17,1±0,4	17,3±0,5	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,95		0,75		
%АКМ, % / *%Active cellular mass,%*	45,2±0,8	46,1±0,8	50,8±0,4	51,4±0,5	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,44		0,3		
ОВ, л / *Total water, l*	26,8±0,9	26,6±0,9	19,7±0,5	19,8±0,5	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,86		0,83		
ООЖ, л / *Total fluid volume, l*	24,7±0,9	24,5±0,9	17,0±0,6	17,3±0,5	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,85		0,72		
ОВнек.Ж, л / *Total extracellular fluid, l*	8,2±0,4	8,0±0,4	6,0±0,2	6,1±0,2	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,75		0,88		
ОВнук.Ж, л / *Total intracellular fluid, l*	16,6±0,5	16,5±0,6	11,0±0,4	11,2±0,4	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,92		0,67		
ОО, ккал / *Basic metabolism, kcal*	1436±24	1436±32	1189±12	1188±13	$p_{12до}$=0,0001* $p_{12после}$=0,0001*
p до/после	0,99		0,94		

Note: * *— statistically significant differences.*
Примечание: * — статистически значимые различия.

Table 2 / Таблица 2

Dynamics of cardiointervalogram during summer health events (M±m)
Динамика кардиоинтервалограмм при летних оздоровительных мероприятиях (M±m)

Показатели *Parameters*	I группа *I group*		II группа *II group*		p
	до / *before*	после / *after*	до / *before*	после/ *after*	
	1	2	3	4	5
ЧСС, уд. мин / *Heart rate, bpm*	76,7±2,6	72,2±3,2	79,8±1,7	77,1±1,5	$p_{12до}$=0,31 $p_{12после}$=0,11
p до/после / *p before/after*	0,25		0,21		
AMo, %	42,4±4,7	38,9±5,2	37,6±2,0	34,1±1,6	$p_{12до}$=0,24 $p_{12после}$=0,22
p до/после	0,6		0,16		
DX, с	0,35±0,03	0,40±0,04	0,36±0,01	0,41±0,01	$p_{12до}$=0,59 $p_{12после}$=0,9
p до/после	0,26		0,03*		
ИН, усл. ед. / *Voltage index*	108,8±23,9	102,7±42,8	82,6±9,2	63,3±6,5	$p_{12до}$=0,2 $p_{12после}$=0,16
p до/после	0,89		0,08		
ИВР, усл. ед. / *Index of vegetative balance*	160,8±32,9	148,9±50,4	117,3±10,8	93,0±8,2	$p_{12до}$=0,09 $p_{12после}$=0,09
p до/после	0,83		0,07		
ВПР, $1/с^2$ / *Vegetative rhythm indicator, $1/s^2$*	4,38±0,57	3,94±0,88	4,05±0,24	3,46±0,19	$p_{12до}$=0,43 $p_{12после}$=0,34
p до/после	0,67		0,05*		
ПАПР, 1/с *Indicator of the adequacy of regulatory processes, 1/s*	56,2±7,4	49,7±9,2	51,9±3,5	45,7±2,8	$p_{12до}$=0,57 $p_{12после}$=0,54
p до/после	0,21		0,16		
SDNN, мс	64,6±9,1	77,2±9,5	65,2±4,2	74,9±3,6	$p_{12до}$=0,94 $p_{12после}$=0,77
p до/после	0,32		0,07		
RMSSD, мс	68,8±11,1	88,0±13,4	68,9±6,0	82,4±5,5	$p_{12до}$=0,99 $p_{12после}$=0,63
p до/после	0,26		0,09		
TP, $мс^2$	4666±1336	6439±1273	4444±706	5782±755	$p_{12до}$=0,88 $p_{12после}$=0,65
p до/после	0,33		0,19		
HF, %	32,3±4,4	30,5±3,8	41,4±2,2	37,7±2,2	$p_{12до}$=0,03* $p_{12после}$=0,08
p до/после	0,74		0,22		
LF, %	36,4±2,5	40,1±2,6	34,5±1,5	36,0±1,6	$p_{12до}$=0,49 $p_{12после}$=0,16
p до/после	0,29		0,47		
VLF, %	31,3±4,1	29,5±3,0	24,1±1,6	26,3±1,9	$p_{12до}$=0,04* $p_{12после}$=0,37
p до/после	0,7		0,3		
LF/HF, ед	1,56±0,28	2,01±0,54	0,96±0,09	1,14±0,12	$p_{12до}$=0,008* $p_{12после}$=0,02*
p до/после	0,43		0,21		
HFnorm, %	44,8±4,3	42,1±4,6	53,9±2,1	50,4±2,1	$p_{12до}$=0,03* $p_{12после}$=0,05*
p до/после	0,65		0,22		
LFnorm, %	55,2±4,3	57,9±4,5	46,1±2,1	49,6±2,1	$p_{12до}$=0,02* $p_{12после}$=0,04*
p до/после	0,65		0,22		

Note: ** — statistically significant differences.*
Примечание: * — статистически значимые различия.

increased. However, the number of errors has also significantly increased. The authors associate this with the fact that the brain motor cortex activity has become higher as shown in the speed of laying and significant intensity of the ball grasp. With this test, children with NSG also showed significantly better results in a decrease in the ball laying intervals and an increase in the ball laying speed.

Discussion

The data analysis showed that summer recreation activities over 2.5 weeks did not lead to significant reliable shifts in the parameters of anthropometry and impedance in children both with oBMI and NSG. At the same time, in children with BMI, the initially significant difference was an excess of adipose mass and a lack of active cell mass. This indicates inadequate protein metabolism and, probably, the diet in children with oBMI. Low values of %ACM are also commonly associated with hypodynamia which a priori is more often inherent in these children.

What shifts in heart rate regulation occur after health improvement? In children of two groups, unidirectional, but insignificant positive shifts are noted: a decrease in heart rate, mode amplitude, %, stress index, VBI, VRI, IARP;

Table 3 / Таблица 3

Dynamics of stabilometry indicators of the test "Simulator "Balls" during summer health events (M±m)
Динамика показателей стабилометрии теста «тренажер «Мячики» при летних оздоровительных мероприятиях (M±m)

Показатели *Parameters*	I группа *I group*		II группа *II group*		P
	до / *before*	после / *after*	до / *before*	после / *after*	
	1	2	3	4	5
Очки, ед / *Points, units*	16,9±0,8	19,5±0,9	16,4±0,6	19,8±0,7	$p_{12до}$=0,68 $p_{12после}$=0,85
p до/после / *p before/after*	0,03*		0,009*		
Ошибки, ед / *Errors, units*	2,13±0,35	2,73±0,48	1,71±0,23	2,35±0,31	$p_{12до}$=0,68 $p_{12после}$=0,85
p до/после	0,03*		0,009*		
Интенсивность захвата (длительность интервалов захвата), с / *Capture intensity (duration of the intervals capture), s*	3,34±0,19	2,83±0,15	3,30±0,11	2,83±0,11	$p_{12до}$=0,84 $p_{12после}$=0,98
p до/после	0,03*		0,003*		
Интенсивность укладки (длительность интервалов укладки), с / *Laying intensity (duration of the intervals of laying), s*	3,08±0,15	2,66±0,18	3,31±0,12	2,72±0,12	$p_{12до}$=0,3 $p_{12после}$=0,77
p до/после	0,07		0,001*		
Интенсивность ошибки (длительность интервалов ошибки), с / *Error intensity (duration of error intervals), s*	2,09±0,38	1,58±0,26	2,71±0,39	1,82±0,23	$p_{12до}$=0,35 $p_{12после}$=0,53
p до/после	0,25		0,06		
Скорость захвата, мм/с / *Capture speed, mm/s*	75,4±3,5	76,3±4,5	77,2±1,9	82,1±2,2	$p_{12до}$=0,63 $p_{12после}$=0,18
p до/после	0,86		0,1		
Скорость укладки, мм/с / *Laying speed, mm/s*	72,4±4,1	73,5±4,6	72,9±2,0	82,5±3,2	$p_{12до}$=0,89 $p_{12после}$=0,12
p до/после	0,84		0,01*		
Скорость ошибки, мм/с / *Error speed, mm/s*	80,0±10,0	78,2±11,6	66,4±6,6	87,3±10,2	$p_{12до}$=0,27 $p_{12после}$=0,6
p до/после	0,9		0,09		

Note: * *— statistically significant differences.*
Примечание: * — статистически значимые различия.

unreliable increase in SDNN and RMSSD. This indicates a general decrease in sympathetic activity. However, only in children with NSG, there was a significant increase in the variation range (DX, s) and VRI which indicates an increase in the parasympathetic activity of regulation. These changes led to the fact that the stress index in this category of children decreases by 30%, in children with oBMI only by 6%. Such changes associated with recreation activities indicate positive sanogenic shifts in heart rhythm regulation.

It is known that postural regulation is associated with the function of many physiological systems of the body and includes sensory and musculoskeletal systems, various levels of the central nervous system. Its effortful control, in contrast to reflex and automatic stem and subcortical reactions, is largely subordinate to consciousness. As can be seen from the data obtained, in children in the health improvement process, the regulation of postural control is significantly optimized, decision-making processes are accelerated especially in children with NSG.

The age of the second childhood or prepubertal period (9–11 years for girls and 10–12 years for boys) is important and interesting as gender differences begin to appear in the physical development parameters, hormonal and vegetative status associated with the background of pronounced individual variability. Therefore, an integrated approach to the recreation activity assessment allows a broader approach to this problem. In the authors' opinion, health improvement will be considered effective not only when the weight of obese children decreases, but also when in children with NSG, a change in body weight will lead to a change not in the level of physical development, but in the processes of body regulation at the level of heart and brain activity.

Conclusion

Thus, the studies performed have shown that the proposed health improvement programs with a non-drug complex of resource provision for a children's sanatorium recreation camp can be assessed not only using the «obligate» indices for the efficacy of health improvement (height, body weight, muscle strength, and vital capacity), which are not can always correctly reflect this process, but also by functional methods of cardiointervalography and stabilometry. They have practical significance and can be recommended for use at recreational and rehabilitation institutions to assess the body's adaptive capabilities.

Financing. *The study did not have sponsorship (mandatory section).*

Источник финансирования. Исследование не имело спонсорской поддержки

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Никитюк Д.Б., Клочкова С.В., Алексеева Н.Т., Рожкова Е.А., Карпова А.В. Конституциональные подходы в оценке физического развития детей // *Всероссийская научно-практическая конференция «Достижения современной морфологии – практической медицине и образованию»*; Май 21-23, 2020; Курск. eLIBRARY ID: 43782144
2. Кондрашев А.В., Соколов В.В., Чаплыгина Е.В., Соколова Н.Г., Осипов Д.П., Елизарова Е.С. Соматотипологическая характеристика подростков и лиц юношеского возраста – жителей Юга России // *Морфология*. – 2008. – Т. 133, № 2. – С. 66. eLIBRARY ID: 11641832
3. Анохин П.К. *Очерки по физиологии функциональных систем*. – М.: Медицина; 1975.
4. Николаев Д.В., Смирнов А.В., Бобринская И.Г., Руднев С.Г. *Биоимпедансный анализ состава тела человека*. – М.: Наука; 2009.
5. Эдлеева А.Г., Хомич М.М., Леонова И.А., Богданов В.А. Биоимпедансометрия как метод оценки компонентного состава тела у детей старше 5 лет // *Детская медицина Северо-Запада*. – 2011. – Т. 2, № 3. – С. 30-35. eLIBRARY ID: 17799923
6. Галеев А.Р., Игишева Л.Н., Казин Э.М. Вариабельность сердечного ритма у здоровых детей в возрасте 6-16 лет // *Вестник ХНУ им. В.Н. Каразина (Серия «Медицина»)*. – 2002. – № 3 (545). – С. 35–40. eLIBRARY ID: 21423661
7. Переяслов Г.А., Слива С.С. Методическое обеспечение стабилоанализатора «СТАБИЛАН – 01» // *Известия ТРТУ. Тематический выпуск*. – 2002. – № 5(28). - С. 82-88. eLIBRARY ID: 12836378

REFERENCES

1. Nikityuk D.B., Klochkova S.V., Alekseeva N.T., Rozhkova E.A., Karpova A.V. Constitutional approaches to assessing children's physical development. *Vserossijskaja nauchno-prakticheskaja konferencija «Dostizheniya sovremennoj morfologii – prakticheskoj medicine i obrazovaniyu»*; Maj 21-23, 2020; Kursk (In Russ.). eLIBRARY ID: 43782144
2. Kondrashev A.V., Sokolov V.V., CHaplygina E.V., Sokolova N.G., Osipov D.P., Elizarova E.S. Somatotypological characteristic of adolescents and youths - inhabitants of the South of Russia. *Morfology*. 2008; 133 (2): 66. (In Russ.). eLIBRARY ID: 11641832
3. Anohin P.K. *Ocherki po fiziologii funkcional'nyh sistem*. Moscow: Medicina; 1975. (In Russ.).
4. Nikolaev D.V., Smirnov A.V., Bobrinskaya I.G., Rudnev S.G. *Bioimpedansnyj analiz sostava tela cheloveka*. Moscow: Nauka; 2009. (In Russ.).
5. Edleeva A.G., Homich M.M., Leonova I.A., Bogdanov V.A. Bioimpedansometriya kak metod ocenki komponentnogo sostava tela u detej starshe 5 let. *Detskaya medicina Severo-Zapada*. 2011;2(3):30-35. (In Russ.). eLIBRARY ID: 17799923
6. Galeev A.R., Igisheva L.N., Kazin E.M. Variabel'nost' serdechnogo ritma u zdorovyh detej v vozraste 6-16 let. *Vestnik HNU im. V.N. Karazina (Seriya «Medicina»)*. 2002;3(545):35–40. (In Russ.). eLIBRARY ID: 21423661
7. Pereyaslov G.A., Sliva S.S. Metodicheskoe obespechenie stabiloanalizatora «STABILAN – 01». *Izvestiya TRTU. Tematicheskij vypusk*. 2002;5(28):82-88. (In Russ.). eLIBRARY ID: 12836378

8. Тришин А.С., Бердичевская Е.М. Стабилографические тренажеры в оценке специфических навыков позной координации у квалифицированных баскетболистов // *Вестник АГУ.* – 2016. – Вып. 1 (176). – С. 55-59. eLIBRARY ID: 26028489
9. Бунак В.В., Нестурх М.Ф., Рогинский Я.Я. *Антропология. Краткий курс.* – М.: Учпедгиз; 1941.

Информация об авторах

Тараканов Александр Викторович, д.м.н., проф., зав. кафедрой скорой медицинской помощи (с курсом военной и экстремальной медицины), Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. E-mail: dr-tarakanov@yandex.ru.

Чаплыгина Елена Викторовна, д.м.н., проф., зав. кафедрой нормальной анатомии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. E-mail: ev.chaplygina@yandex.

Елизарова Елена Сергеевна, к.м.н., доцент кафедры нормальной анатомии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. E-mail: el02@bk.ru.

Тараканова Татьяна Дмитриевна, к.м.н., доцент кафедры детских болезней №2, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. E-mail: dr-tarakanov@yandex.ru.

Коршунов Олег Васильевич, невролог, Детский санаторный оздоровительный лагерь «Мир», Ростовская область, Россия. E-mail: doctor@center-mir.ru.

Вклад авторов:

А.В. Тараканов, Е.В. Чаплыгина — разработка дизайна исследования;

А.В. Тараканов, Е.В. Чаплыгина — написание текста рукописи;

Е.С. Елизарова, О.В. Коршунов — сбор материала;

А.В. Тараканов, Т.Д. Тараканова — анализ данных;

Т.Д. Тараканова, Е.С. Елизарова — обзор публикаций по теме статьи.

Получено / Received: 01.12.2020
Принято к печати / Accepted: 28.01.2021

8. Trishin A.S., Berdichevskaya E.M. Stabilograficheskie trenazhery v ocenke specificheskih navykov poznoj koordinacii u kvalificirovannyh basketbolistov. *Vestnik AGU*. 2016;1(176):55-59. (In Russ.). eLIBRARY ID: 26028489
9. Bunak V.V., Nesturh M.F., Roginskij YA.YA. *Antropologiya. Kratkij kurs.* Moscow: Uchpedgiz; 1941. (In Russ.).

Information about the authors

Alexander V. Tarakanov, Dr. Sci. (Med.), Professor, head of department of emergency medicine (with a course of military and extreme medicine), Rostov state medical University, Rostov-on-Don, Russia. E-mail: dr-tarakanov@yandex.ru.

Elena V. Chaplygina, Dr. Sci. (Med.), Professor, head of department of normal anatomy, Rostov state medical University, Rostov-on-Don, Russia. E-mail: ev.chaplygina@yandex.

Elena S. Elizarova, Cand. Sci. (Med.), docent of department of normal anatomy, Rostov state medical University, Rostov-on-Don, Russia. E-mail: el02@bk.ru.

Tatyana D. Tarakanova, Cand. Sci. (Med.), docent of department of children's diseases № 2, Rostov state medical University, Rostov-on-Don, Russia. E-mail: dr-tarakanov@yandex.ru.

Oleg V. Korshunov, neurologist, Children's sanatorium health camp «Mir», Rostov region, Russia. E-mail: doctor@center-mir.ru.

Authors contribution:

A.V. Tarakanov, E.V. Chaplygina — research design development;

A.V. Tarakanov, E.V. Chaplygina — writing the text of the manuscript;

E.S. Elizarova, O.V. Korshunov — data acquisition;

A.V. Tarakanov, T.D. Tarakanova — data analysis;

T.D. Tarakanova, E.S. Elizarova — review of publications on the topic of the article.

УДК: 616.131-007.2: 616.231-007.271-089
DOI 10.21886/2219-8075-2021-12-1-82-88

A case of timely diagnosis and successful surgical correction of the left pulmonary artery sling in a newborn

M.G. Pukhtinskaya, V.V. Estrin, A.A. Lebedenko, Yu.A. Porutchikova, A.V. Simonova, T.N. Aleksanyants

Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia

The article describes a clinical observation of a newborn patient with a rare congenital cardiovascular disorder of the left pulmonary artery sling. There are few publications in the world's literature on the clinical observations of the above pathology, which causes the key difficulty in diagnostics. Moreover, this case features a favorable outcome thanks to a timely diagnosis and a successful surgical correction that followed.

Keywords: sling complex, left pulmonary artery disorder, newborn, respiratory distress, artificial pulmonary ventilation.

For citation: Pukhtinskaya M.G., Estrin V.V., Lebedenko A.A., Porutchikova Yu.A., Simonova A.V., Aleksanyants T.N. A case of timely diagnosis and successful surgical correction of the left pulmonary artery sling in a newborn. *Medical Herald of the South of Russia.* 2021;12(1):82-88. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-82-88.

Corresponding: Marina G. Pukhtinskaya, puhmar@mail.ru.

Случай своевременной диагностики и успешной хирургической коррекции слинга левой легочной артерии у новорожденного

М.Г. Пухтинская, В.В. Эстрин, А.А. Лебеденко, Ю.А. Порутчикова, А.В. Симонова, Т.Н. Алексанянц

Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия

Представлено клиническое наблюдение новорожденной пациентки с чрезвычайно редким врождённым сердечно-сосудистым пороком — слингом левой лёгочной артерии. В мировой научной литературе существует весьма ограниченное количество публикаций, посвященных клиническому наблюдению этой патологии, что и остается основной причиной, определяющей сложность диагностики. Кроме того, особенностью данного случая является его благоприятный исход ввиду своевременной диагностики и последующей успешной хирургической коррекции.

Ключевые слова: слинг комплекс, аномалии левой лёгочной артерии, новорожденный, дыхательная недостаточность, искусственная вентиляция лёгких.

Для цитирования: Пухтинская М.Г., Эстрин В.В., Лебеденко А.А., Порутчикова Ю.А., Симонова А.В., Алексанянц Т.Н. Случай своевременной диагностики и успешной хирургической коррекции слинга левой легочной артерии у новорожденного. *Медицинский вестник Юга России.* 2021;12(1):82-88. DOI 10.21886/2219-8075-2021-12-1-82-88.

Контактное лицо: Пухтинская Марина Гаевна, puhmar@mail.ru.

Despite rare occurrence in clinical practice (1:14,000 newborns), the left pulmonary artery sling is one of the "classic" causes of respiratory insufficiency in children associated with a congenital cardiovascular pathology [1].

Anatomically, a sling is an anomaly in which the left pulmonary artery originates from the right pulmonary artery and goes between the trachea and esophagus. The form "vascular loop" compresses and deforms the rings of the trachea and sometimes the bronchus [1, 2]. Often, a comorbid congenital pathology of the heart and the tracheobronchial tree is diagnosed. Thus, the main symptoms of the disease are such clinical signs of respiratory insufficiency as cyanosis, expiratory or combined dyspnea, and tachyarrhythmia. Sometimes, the disease develops symptomless. The first description of the results of the autopsy of a patient with this anomaly was made by Glaevecke and Doehle (1897) [3]. It is believed that the term "left pulmonary artery sling" has been used in clinical practice since 1958 [4].

The treatment for this congenital pathology is only surgical [5]. Without surgical correction, the disease

prognosis is unfavorable [6–8]. The first surgical correction of the left pulmonary artery sling was performed by Willis J. Potts in 1953.

The article describes a rare clinical case of a newborn with the left pulmonary artery sling, diagnostics, and a successful surgical correction.

Female child Ch. was born on October 10, 2020 at a delivery department of the Central Municipal Hospital by a 30-year-old mother with a burdened obstetric-gynecologic anamnesis (uterine scar, candida colpitis), mixed type vegetative-vascular dystonia, first-degree obesity, and chronic nicotine addiction. The mother had 4 pregnancies (2 artificial abortions in the anamnesis) with prelabor rupture of membranes; 2 abdominal deliveries (uterine scar, large fetus) at 38 weeks and 2 days. The fetus weight was 4000 g, 7-7 score by the Apgar scale, in a condition of moderate severity associated with neurologic symptoms (decreased reaction during examination, weak crying, muscular hypotonia, hyporeflexia).

The worsening of the condition was observed within the first day after the birth. Clinical symptoms of respiratory insufficiency appeared (grunting breathing with the involvement of additional muscles, intercostal retraction, nasal flaring, mixed dyspnea to 60 per minute, a decrease in saturation to 90–91%, weakening of breathing in the lungs). Respiratory therapy started that included a facial oxygen mask O_2 5 L/min. The condition of the newborn continued worsening (score 4 by the Downes scale): dyspnea more than 70/minute, the appearance of bilateral crepitate rales, which required transfer to continuous positive airway pressure via nasal cannulas (positive end-expiratory pressure +5 mm H_2O; O_2 – 50%).

The indicated therapy did not stabilize the condition of the child. On October 11, 2020, the child was examined by a resuscitator, got intubated, and transferred to the Department of Intensive Care at the Scientific and Research Institute of Obstetrics and Pediatrics for artificial pulmonary ventilation (APV). The child was transported in a warmed transport incubator by a critical care transport ambulance. The diagnosis at admission was perinatal hypoxia, respiratory distress syndrome, congenital pneumonia?

The condition of the child at admission was severe. The severity was associated with respiratory insufficiency and neurologic symptoms. Heart rate HR = 156 bpm, t = 36.6 °C, StO_2 = 92%, blood pressure BP = 60/34 mmHg. Clinically: decreased reaction to examination. Spontaneous breathing activity was decreased. Bregmatic fontanel (2.5 × 2.0 cm) was not tensed, the sagittal suture was open. Muscular hypertonia and dystonia were observed. Reflexes of oral and spinal automatism were weak. Meningeal symptoms were not revealed. The pupillary diameter was normal, D = S; reaction to light was active and consensual. Horizontal spontaneous nystagmus was observed. The skin was pale pink; perioral acrocyanosis was reduced after oxygen therapy. Pastosity of the face and eyes was registered. Visible mucosae were wet and pink. Heart tones were muffed and rhythmic. The pulse strength and volume were satisfactory. Hemodynamics was stable. The child was on APV, adapted with the apparatus. By auscultation, breathing was detected in all the lobes. Breathing was weak in the posterior-inferior sections. The rales were not heard. The abdomen was soft, not swallowed, painless at palpation. The liver was +2.0 cm from the edge of the costal arch. The spleen was not palpated. Urination was unassisted, urine was light yellow. The stool was unassisted, meconium, without pathologic matter. At admission, the child was preliminarily diagnosed with cerebral ischemia (P91.0) and respiratory distress syndrome of the newborn (P28.5). Taking into account the mother's anamnesis, the congenital infection could not be excluded.

At admission, the results of laboratory and instrumental studies showed:

- Complete blood count (CBC): leucocytes – 10.5×10^9/L; hemoglobin – 162 g/L; erythrocytes – 4.52×10^{12}/L; hematocrit – 47.0%; platelet – 219×10^9/L;
- capillary blood pH: parameters were balanced, lactatemia 2.7;
- common urine analysis – without pathology;
- blood biochemistry: hypoglycemia – 1.4 mmol/L, hypoproteinemia – 41.4 g/L, hypoalbuminemia – 28.7 g/L, bilirubinemia – 57.3 μmol/L due to indirect filtration;
- coagulogram – normal;
- chest and abdominal X-ray – moderate, bilateral increased pulmonary vascularity (Figure 1), intestinal hyper pneumatization;
- neurosonogram – signs of external hydrocephalus, ischemia, intraventricular hemorrhage (IVH) stage 1–2.
- Ultrasonography of the heart – patent foramen ovale 2.2 mm, left-to-right shunting, the systolic function of the left ventricle was preserved; Doppler sonography of brain vessels – vascular plexus of enhanced echo-density, the structure was inconsistent, contours were uneven, vein of Galen – 4.71 cm/s;
- ultrasonography of internal organs – enlarged liver, changes in the parenchyma, neurologist's examination – cerebral ischemia, IVH 1–2.

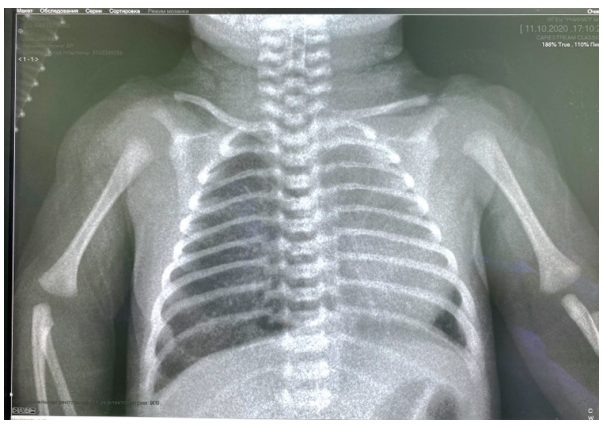

Figure 1. Chest X-ray at admission.
Рисунок 1. Рентгенография лёгких при поступлении.

At the department of resuscitation, the child underwent combined multicomponent intensive therapy. Respiratory therapy – sequentially, stage by stage: high-frequency ventilation (HFV); HFV with iNO 5 ppm; APV with standard parameters, high-flow nasal cannulas (HFNC); spontaneous breathing through an oxygen mask.

Antibiotic therapy (initial with further change) – by the decision of a multidisciplinary team meeting, for health reasons, considering the sensitivity of the isolated microflora, clinical symptoms, and written consent of patients.

Hemostatic therapy: vicasol, dicynone. Infusion-transfusion therapy: correction of hypocoagulation – native quarantine fresh-frozen plasma B(III)Rh+; correction of anemia – washed erythrocytes B(III)Rh+; correction of hypoproteinemia, hypoalbuminemia – albumin 10%; parenteral nutrition – glucose solution 20%, 10% with components, aminoven 10%, smooth lipid 20%. Adaptation with an APV apparatus – sodium oxybate i.v./by drop infusion. Phototherapy. Inhalation therapy: ipratropium, pulmicort. Enteral tube nutrition every 3 hours with Pre-Nan infant formula.

Despite the therapy, the patient's condition remained severe. The severity of the condition was provided by respiratory insufficiency, symptoms of bacterial infection (pale, icteric skin, expressed vascular pattern on the anterior abdominal wall) associated with diminished breathing (primary, on the right side), bilateral crepitate rales, trachea produced significant amount of liquid, mucopurulent sputum, enlargement of the liver and spleen. CBC showed anemia, neutrophil leukocytosis to 26×10^9/L with a shift to stab, monocytosis. A common urine test showed protein and leukocyturia. Biochemistry of the blood showed hypoprotein-hypoalbuminemia, bilirubinemia primarily due to indirect fraction, an increase in the activity of aspartate transaminase; hypocoagulation. The acid-base balance of capillary blood in the dynamics revealed hypoxemia, persistent hypercapnia, lactatemia. Procalcitonin in the blood in the dynamics varied from 0.5 to >10 μg/L; C-reactive protein was not revealed. Bacteriologically: endotracheal tube, pharynx mucosa, nose – growth of *Acinetobacter baumannii* 1×10^6 CFU/ml (polyresistance to all antibiotics); *Staphylococcus haemolyticus* 1×10^6 CFU/ml; blood – growth of *Staphylococcus epidermidis*.

On October 17, 2020, considering severe condition, X-ray imaging of the lungs in dynamics was made. Atelectasis of the segment of the right upper lobe was diagnosed. The bronchovascular pattern was enhanced along both pulmonary fields (Figure 2).

Therapeutic-diagnostic bronchoscopy was performed, which revealed dystopia of the trachea, catarrhal-mucous endobronchitis, expressed symmetrical slit-like narrowing of the right main bronchus to 1–2 mm. X-ray control: positive dynamics – lack of visualization of atelectasis in the right upper lobe, left-right asymmetric pattern of the visceral organs (the mediastinum was off-centered to the left and closed the left lung). Subsegmental atelectasis of the upper lobe of the left lung cannot be excluded.

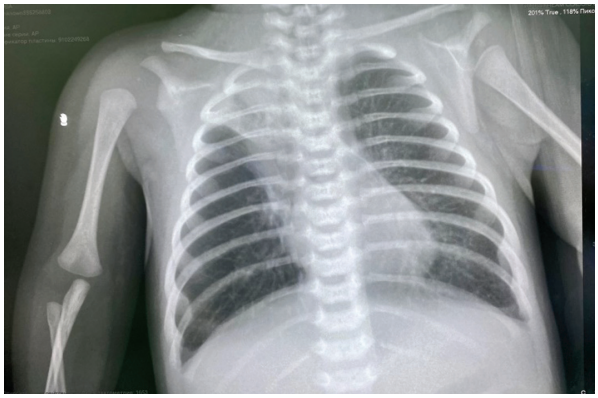

Figure 2. X-ray of the lungs in dynamics; atelectasis of the right upper lobe.
Рисунок 2. Рентгенография легких в динамике; ателектаз правой верхней доли.

On October 29, 2020, the condition of the patient was severe and stable. Supportive APV by continuous mandatory ventilation at a respiratory rate of 20/min; O_2-30%. HR = 142 bpm, t = 36.6 °C, StO_2 = 96%, BP = 73/44 mm Hg. Clinically, weak breathing remained, bilateral dry rales, a significant amount of liquid sputum expressed from the trachea. Considering the transportability of the patient, computed tomography (CT) of the chest was performed at the Regional Clinical Hospital for Children. Fibroatelectasis of the right upper lode was diagnosed. Fibrous alterations in S_{10} of the lower lobe of the left lung with inflammatory alterations (Figure 3) were revealed. Obstruction of the right main bronchus 1.0 cm lower than the bifurcation was observed (Figures 4, 5). At the same time, emphysematous dilation of the lower lobe of the right lung with a moderate off-center shift of mediastinal organs to the left was observed. Examination of the pediatric surgeon: congenital anomaly of the right lung. Therapeutic bronchoscopy was recommended. Surgical treatment at the time of examination was not required.

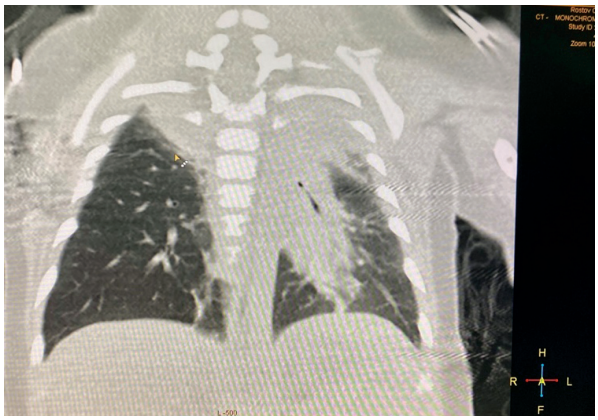

Figure 3. CT scan; fibroatelectasis of the right upper lobe; inflammatory changes in the left lung; narrowing of the left bronchus.
Рисунок 3. Компьютерная томография; фиброателектаз правой верхней доли; воспалительные изменения в левом лёгком; сужение левого бронха.

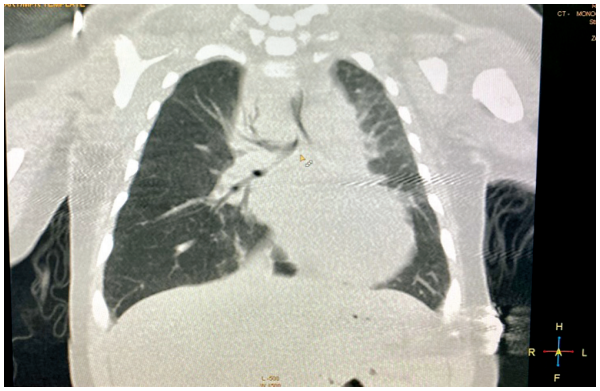

Figure 4. CT scan; narrowing of the trachea and main bronchus on the right.
Рисунок 4. Компьютерная томография; сужение трахеи и главного бронха справа.

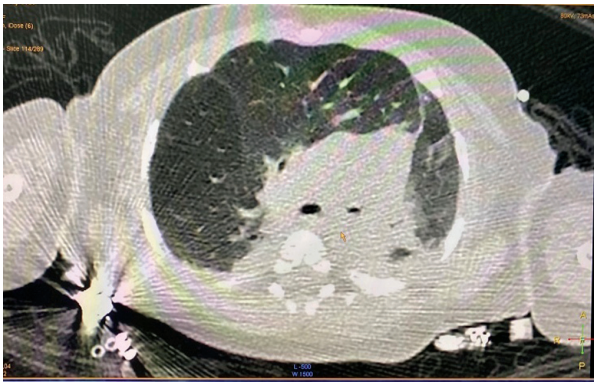

Figure 5. CT scan; narrowing of the right bronchus.
Рисунок 5. Компьютерная томография; сужение правого бронха.

On November 3, 2020, telemedical consulting of the patient was performed by cardiologists and surgeons from the State Pediatric Medical University (Saint Petersburg). The ultrasonography of the heart and vessels was recommended to exclude the vascular ring formed by aberrant veins and arteries. CT of mediastinal vessels in the vascular mode was recommended to exclude the exterior compression of the trachea and bronchus.

Positive dynamics were noted during the therapy: the patient was extubated and switched to spontaneous breathing via HFNC, later via a facial oxygen mask. Clinically: the skin was pink, mixed dyspnea 57/min, breathing with accessory muscles of respiration, moderate intercostal retraction. Lung auscultation: the breathing is heard with single rales on the left. On the right, in the projection of the upper lobe, the breathing was weak. In the projection of the middle lower lobe, every 2–3 respiratory movements, hissing breathing with a specific click was heard.

On December 3, 2020, at the cardio surgical department of the Rostov Regional Clinical Hospital, spiral CT with angiography of the chest was performed. Conclusion: a sharp narrowing of the distal section of the trachea to 2 mm (in the area of the bifurcation), narrowing of the right main bronchus to 1 mm (3.5 mm long). The left main bronchus was narrowed to 1.5 mm.

The lung artery (10.7 mm in diameter) coursed from the right ventricle. The stem was at the level of the bifurcation (12.5 mm). The right pulmonary artery was 9.7 mm. The left pulmonary artery was up to 5 mm, coursed from the right pulmonary artery, and looped over the right main bronchus and trachea constricting them.

On December 16, 2020, considering the diagnosed cardiovascular anomaly, the child was examined by a telemedical line and transported to the Saint Petersburg State Pediatric Medical University of the Ministry of Healthcare of the Russian Federation to the Intensive Care Unit for children with cardiosurgical pathology for further surgical treatment.

The primary clinical diagnosis: IDC-10: Q25.7: Congenital heart defect: Other congenital malformations of the pulmonary artery (left pulmonary artery sling), bronchi congenital defect. The complication of the primary disease: fibroatelectasis of the upper lobe of the right lung.

Comorbid diseases: early residual-organic lesion of the central nervous system, atrophic hydrocephalus syndrome, IVH stage 2, at the stage of organization, neonatal sepsis caused by other staphylococci, bilateral pneumonia, period of remission.

Discussion

On December 24, 2020, at the Saint Petersburg State Pediatric Medical University, the patients with a clinical diagnosis Q25.7 Congenital heart defect: left pulmonary artery sling; open arterial duct, compression of the right main bronchial ostium underwent successful surgery: re-implantation of the left pulmonary artery into the stem of the pulmonary artery in the condition of artificial circulation.

On January 15, 2021, the patient was discharged from the hospital in a satisfactory stable condition for a follow-up by a local pediatrician (Figure 6).

The presented clinical case confirmed complicated diagnostics of the left pulmonary sling, especially, in the neonatal period. APV, severe bacterial complications, complicated or often impossible use of highly informative methods of diagnostics in the specialized conditions considering the “non-transportability” of patients, a requirement for consultations with various medical specialists, lack of “medical vigilance” and clinical experience because of the rare occurrence of the pathology determine the actual condition of the problem.

A thorough analysis of the development of the disease allowed the authors to make the following conclusions. In this case, the main signs within the symptom complex that suggested the left pulmonary artery sling included persistent weakening of breathing on the right (affected side), a significant volume of liquid mucous sputum during the ob-

servation, persistent hypercapnia, a necessity in long-term APV, atelectasis of the upper lobe of the right lung, and narrowing of the right main bronchus.

Figure 6. Patient Ch. after radical correction of the left pulmonary artery sling (photo is published with the written permission of the patient's mother).
Рисунок 6. Пациентка Ч. после радикальной коррекции слинга левой легочной артерии (фотография публикуется с письменного разрешения матери).

The only effective method of treatment for this congenital cardiovascular defect is the surgical correction of the pulmonary loop, which is performed "open"-hearted with artificial blood circulation. This involves the transportation and hospitalization of the patient to a cardio surgical specialized inpatient center [1–8]. It is evident that in these conditions, the success of this surgery with a favorable outcome is multifactor and ambiguous.

In this case, a favorable outcome of the correction of the left pulmonary artery sling in the patient was provided by the timely highly informative diagnostics that included fibrobronchoscopy, CT with angiography, cooperation of various specialists, telemedical counseling, careful transportation, high professionalism, and personal involvement.

Conclusion

The presented clinical case has confirmed that currently, a favorable outcome of the treatment for the left pulmonary artery sling in a newborn is possible when combined highly technological diagnostic, intensive care, and surgical help are provided. CT with vessels contrasting is the method of choice if the pulmonary artery sling is suspected.

Although this pathology is rare, neonatologists and resuscitators should have clinical vigilance for the possibility of this cardiovascular pathology. A clinical protocol for the management of a neonate with the left pulmonary artery sling should be developed and implemented.

Financing. *The study did not have sponsorship (mandatory section).*

Источник финансирования. Исследование не имело спонсорской поддержки

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

ЛИТЕРАТУРА

1. Базылев В.В., Черногривов А.Е., Черногривов И.Е. Аберрантное отхождение левой ветви легочной артерии, стеноз трахеи и ринг-слинг комплекс (Часть I). // *Бюллетень НЦССХ им. А.Н. Бакулева РАМН.* – 2018. - №19(1). – С.14-27. DOI: 10.24022/1810-0694-2018-19-1-14-27
2. Бокерия Л.А., Свободов А.А., Никифоров В.С., Адкин Д.В., Юрпольская Л.Ю. Случай успешной коррекции аномального отхождения левойлегочной артерии (слинг) с дефектом межжелудочковой перегородки у ребенка в возрасте 6 месяцев. // *Детские болезни сердца и сосудов.* – 2010. - №3. – С.68–9. eLIBRARY ID: 15269318
3. Ким А.И., Акатов Д.С., Макаренко В.Н., Мумладзе К.В., Никифоров В.С. Случай успешной коррекции аномального отхождения левой легочной артерии от правой легочной артерии с бужированием стеноза трахеи. // *Детские болезни сердца и сосудов.* – 2012. - №4. – С.68–9. eLIBRARY ID: 18981625
4. Шаталов К.В., Разумовский А.Ю., Арнаутова И.В., Турдиева Н.С. Хирургическая коррекция слинга левой легочной артерии в сочетании со стенозом трахеи у детей раннего возраста. // *Детские болезни сердца и сосудов.* – 2015. - № 2. – С. 34–8. eLIBRARY ID: 25008655
5. Разумовский А.Ю., Афуков И.И., Кулаев А.Д., Алхасов А.Б., Митулов З.Б., и др. Скользящая трахеопластика у

REFERENCES

1. Bazylev V.V., Chernogrivov A.E., Chernogrivov I.E. Aberrant origin of the left pulmonary artery, congenital tracheal stenosis and ring-sling complex (part I). *Byulleten' Nauchnogo Tsentra Serdechno Sosudistoy Khirurgii imeni A.N. Bakuleva RAMN (Bulletin of Bakoulev Scientific Center for Cardiovascular Surgery RAMS).* 2018;19(1):14–27. (In Russ.). DOI: 10.24022/1810-0694-2018-19-1-14-27
2. Bockeria L.A., Svobodov A.A., Nikiforov V.S., Adkin D.V., Yurpol'skaya L.Yu. The case of successful correction of abnormal left pulmonary artery(sling) with an interventricular septal defect in achild aged 6 months. *Detskie Bolezni Serdtsa i Sosudov (Children's Heart and Vascular Diseases).* 2010;3:68–69. (In Russ.). eLIBRARY ID: 15269318
3. Kim A.I., Akatov D.S., Makarenko V.N., Mumladze K.V., Nikiforov V.S. The case of successful correction of an abnormal departure of the leftpulmonary artery from the right pulmonary arterywith stenosis of the trachea. *Detskie Bolezni Serdtsa i Sosudov (Children's Heart and Vascular Diseases).* 2012;4:68–9. (In Russ.). eLIBRARY ID: 18981625
4. Shatalov K.V., Razumovskiy A.Yu., Arnautova I.V., Turdieva N.S. Surgical correction of the left pulmonary artery sling in combination with trachealstenosis in young children. *Detskie Bolezni Serdtsa i Sosudov (Children's Heart and Vascular Diseases).* 2015;2:34–8. (In Russ.). eLIBRARY ID: 25008655

детей в условиях экстракорпоральной мембранной оксигенации (первый опыт в России) (с комментарием). // *Хирургия. Журнал им. Н.И. Пирогова*. – 2015. - №8. – С. 4–13. DOI: 10.17116/hirurgia201584-13

6. Giudici V., Kanani M., Muthialu N., Carr M., Calder A.M., et al. Duplicated left pulmonary artery: an unknown disease? Three casereports and review of the literature. // *Cardiol. Young*. – 2016. – V. 26(2). – P. 340–6
7. Butler C.R., Speggiorin S., Rijnberg F.M., Roebuck D.J., Muthialu N., et al. Outcomes of slide tracheoplasty in 101 children: a 17-year single-center experience. // *J. Thorac. Cardiovasc. Surg*. – 2014. – V. 147 (6). – P. 1783–9. DOI: 10.1016/j.jtcvs.2014.02.069
8. Speggiorin S., Torre M., Roebuck D.J., McLaren C.A., Elliott M. A new morphologic classification of congenital tracheobronchial stenosis. // *J. Ann. Thorac. Surg*. – 2012. – V. 93. – P. 958–61. DOI: 10.1016/j.athoracsur.2011.12.019.

5. Razumovskiy A.Yu., Afukov I.I., Kulaev A.D., Alkhasov A.B., Mitulov Z.B., Kulikova N.B., Stepanenko N.S. Sliding tracheoplasty in childrenunder conditions of extracorporeal membrane oxygenation (The first experience in Russia) (withcomments). *Khirurgiya. Zhurnal imeni N.I. Pirogova (N.I. Pirogov Journal Surgery)*. 2015; 8: 4–13. (In Russ.). DOI: 10.17116/hirurgia201584-13
6. Giudici V, Kanani M, Muthialu N, Carr M, Calder AD, et al. Duplicated left pulmonary artery: an unknown disease? Three case reports and review of the literature. *Cardiol Young*. 2016;26(2):340-6. DOI: 10.1017/S1047951115000281
7. Butler CR, Speggiorin S, Rijnberg FM, Roebuck DJ, Muthialu N, et al. Outcomes of slide tracheoplasty in 101 children: a 17-year single-center experience. *J Thorac Cardiovasc Surg*. 2014;147(6):1783-9. DOI: 10.1016/j.jtcvs.2014.02.069
8. Speggiorin S, Torre M, Roebuck DJ, McLaren CA, Elliott MJ. A new morphologic classification of congenital tracheobronchial stenosis. *Ann Thorac Surg*. 2012;93(3):958-61. DOI: 10.1016/j.athoracsur.2011.12.019.

Информация об авторах

Пухтинская Марина Гаевна, д.м.н., Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID: 0000-0001-5530-2194; puhmar@mail.ru.

Эстрин Владимир Владимирович, профессор, д.м.н., Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID:0000-0002-9201-8333, medinsur@aaanet.ru.

Порутчикова Юлия Александровна, главный врач, Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID: 0000-0002-7394-6521, ulyagabriel@mail.ru.

Лебеденко Александр Анатольевич, профессор, д.м.н., директор (проректор) Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID: 0000-0003-4525-1500; leb.rost@rambler.ru.

Симонова Анна Валерьевна, к.м.н., заведующая отделением реанимации, Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID: 0000-0001-6951-1827; anuta84@hotmail.com.

Алексанянц Татьяна Николаевна, врач анестезиолог-реаниматолог высшей категориотделения реанимации, Научно-исследовательский институт акушерства и педиатрии, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID ID: 0000-0002-1148-2151, Mariya-aleksanyanc@yandex.ru.

Information about the authors

Marina G. Pukhtinskaya, Dr. Sci. (Med.), Leading Researcher of Department of Anesthesiology and Resuscitation, Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0001-5530-2194; puhmar@mail.ru.

Vladimir V. Estrin, Dr. Sci. (Med.), Professor, Head of Department of Anesthesiology and Resuscitation, Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0002-9201-8333, Rostov-on-Don, medinsur @ aaanet.ru.

Alexander A. Lebedenko, Dr. Sci. (Med.), Professor, Director (Vice-Rector), Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0003-4525-1500; leb.rost@rambler.ru.

Yulia A. Porutchikova, Chief Medical Officer Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0002-7394-6521, ulyagabriel@mail.ru.

Anna V. Simonova, Cand. Sci. (Med.), Manager of Intensive Care unit SRIOP, Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0001-6951-1827; anuta84 @ hotmail.com.

Tatyana N. Aleksanyants, anesthesiolog-resuscitator the highest category of Intensive Care unit SRIOP, Scientifically Research Institute of Obstetrics and Pediatrics, Rostov State Medical University, Rostov-on-Don, Russia. ORCID ID: 0000-0002-1148-2151, Mariya-aleksanyanc@yandex.ru.

Вклад авторов

Все представленные авторы внесли существенный вклад в концепцию и дизайн исследования, получение, анализ данных и их интерпретацию; принимали участие в написании статьи или существенной переработке ее важного научного и интеллектуального содержания; окончательном утверждении версии для публикации.

Все представленные авторы согласны нести ответственность за все аспекты работы и гарантировать соответствующее рассмотрение и решение вопросов, связанных с точностью и добросовестностью всех частей работы.

Получено / Recived: 02.02.2021
Принято к печати / Accepted: 03.03.2021

Authors contribution

All presented authors made significant contributions to the concept and design of the study, data acquisition, analysis and interpretation; took part in the writing of the article or significant revision of its important scientific and intellectual content; final approval of the version for publication.

All submitted authors agree to be responsible for all aspects of the work and to ensure appropriate consideration and resolution of issues related to the accuracy and conscientiousness of all parts of the work.

УДК: 614.23:331.361:378.2
DOI 10.21886/2219-8075-2021-12-1-89-97

Наставничество в Ростовском-на-Дону противочумном институте и информационная связь поколений

И.А. Щипелева, Е.И. Марковская, О.Ф. Кретенчук, О.С. Чемисова

Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия

В статье представлен опыт использования наставничества как наиболее эффективного метода адаптации новых сотрудников для полноценного включения их в работу Ростовского-на-Дону противочумного института. Целью было провести анализ работы по наставничеству в Ростовском-на-Дону противочумном институте и сравнить опыт института с работой в этом направлении в других учреждениях в России и за рубежом. Процесс наставничества очень важен при работе с возбудителями I–II групп патогенности, в том числе в период борьбы с новой коронавирусной инфекцией COVID-19. Также отмечено значение наставничества при погружении в научную среду при мотивации к получению новых знаний и стремлению к инновационному результату в собственных исследованиях.

Ключевые слова: наставничество, адаптация, биологическая безопасность, наставник, наставляемый.

Для цитирования: Щипелева И.А., Марковская Е.И., Кретенчук О.Ф., Чемисова О.С. Наставничество в Ростовском-на-Дону противочумном институте и информационная связь поколений. *Медицинский вестник Юга России.* 2021;12(1):89-97. DOI 10.21886/2219-8075-2021-12-1-89-97.

Контактное лицо: Марковская Елена Ивановна, markovskay2014@yndex.ru.

Mentoring in the Rostov-on-Don anti-plague institute and information link between generations

I.A. Shchipeleva, E.I. Markovskaya, O.F. Kretenchuk, O.S. Chemisova

Rostov-on-Don Anti-plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia

The article presents the experience of using mentoring as the most effective method of adapting new employees to fully include them in the work of the Rostov-on-don anti-plague Institute. The purpose of the study was to analyze the work on mentoring in the Rostov-on-Don anti-plague Institute and to compare the experience of the Institute with the work in this direction in other institutions in Russia and abroad. It was shown how important the mentoring process was when working with pathogens of groups I–II of pathogenicity, including during the fight against the novel coronavirus infection COVID-19. The importance of mentoring when immersed in the scientific environment, when motivating to acquire new knowledge, and striving for innovative results in their research was also noted. Mentoring is a modern method of personnel work that provides quick adaptation, professional development, and career growth, and has a positive effect on the stability of the institution as a whole.

Keywords: mentoring, adaptation, biosecurity, mentor, mentee.

For citation: Shchipeleva I.A., Markovskaya E.I., Kretenchuk O.F., Chemisova O.S. Mentoring in the Rostov-on-Don anti-plague institute and information link between generations. *Medical Herald of the South of Russia.* 2021;12(1):89-97. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-89-97.

Corresponding author: Elena I. Markovskaya, markovskay2014@yndex.ru.

Послушайте — и вы забудете,
посмотрите — и вы запомните,
сделайте — и вы поймете.
Конфуций

Осуществление рабочего процесса на любом предприятии для достижения успехов и процветания требует усилия всех структур данного учреждения в учебном, научном и производственном аспектах. Одной из основных составляющих высокой результативности труда является опыт поколений, который оставили нам предшественники, и возможность перенять его с помощью специалистов с определённым багажом практических и теоретических знаний.

В современной литературе наставничество рассматривается как практика развития персонала трудового коллектива, направленная на формирование уникальных знаний, навыков и компетенций сотрудников, развития их потенциала, формирования поведенческих моделей, соответствующих целям развития данной организации

[1]. В литературе отображена актуальность института наставничества в современной системе образования, проведён анализ потребности молодых специалистов в наставниках [2]. Установлено, что повысить результативность профессионального образования возможно, применяя педагогический потенциал такого феномена, как «наставничество» с использованием интегративной деятельности наставника при решении педагогических задач [3]. Рассматриваются новый смысл процесса и его новая миссия, которая заключается в подготовке специалистов новой формации, использующих современные инновационные подходы, системы и методы педагогики [4]. Наставник, передающий не только опыт, но и традиции, культуру профессии, снова востребован в современном мире [5]. Большое внимание в литературе уделяется развитию наставничества как методу управления знаниями, в корпоративной среде различных современных организаций. Знания, не закреплённые письменно в корпоративных документах, существуют в каждой организации и эффективнее всего передаются неформальным путём. Именно наставничество и является инструментом передачи и знаний, и опыта [6]. Для совершенствования системы управления персоналом на предприятиях авторы проводят анализ, сравнение и обобщение данных в схеме адаптации и развития персонала [7, 8]. Показано недостаточное использование этой составляющей в некоторых российских организациях по сравнению с иностранными, даны различные рекомендации по внедрению наставничества [9]. Описаны интересные факты изучения примеров для подражания и преемственности традиций в творческой среде [10].

Помимо традиционной модели наставничества (наставничество «один на один»), за рубежом появились совершенно новые, распространённые в современной практике, модели наставничества, которые предлагают развивать и в российских компаниях. К таким моделям относится ситуационное наставничество, партнёрское, групповое наставничество, краткосрочное или целеполагающее наставничество, скоростное, флэш-наставничество, виртуальное наставничество, саморегулируемое, реверсивное наставничество и даже командное наставничество [11]. Администрация института с интересом ознакомилась с такими разновидностями процесса обучения молодого поколения и оценила их применительно к опыту работы в институте.

Цель исследования — провести анализ работы по наставничеству в Ростовском-на-Дону противочумном институте и сравнить опыт института с работой в этом направлении в других учреждениях в России и за рубежом.

Анализ осуществления наставничества в институте проведён в соответствии с СП 1.3.3118-13 Безопасность работы с микроорганизмами I–II групп патогенности (опасности), а также на основании Приказа Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека от 12 ноября 2012 г. № 1088 «Об организации наставничества в территориальных органах Роспотребнадзора и подведомственных организациях» и в соответствии с Положением о наставничестве в научно-исследовательских подразделениях Федерального казённого учреждения здравоохранения «Ростовский-на-Дону ордена Трудового Красного Знамени научно-исследовательский противочумный институт». Использованы литературные источники, применено сравнительное аналитическое исследование.

В коллективе Ростовского-на-Дону противочумного института применяется традиционная модель наставничества: проводится подбор наставников и их подопечных по определенным критериям, таким как опыт, навыки, личностные характеристики и другие. Как правило, между наставником и подопечным устанавливаются тесные личные отношения, которые помогают обеспечить заинтересованный индивидуальный подход к сотруднику, создавая комфортную обстановку для его развития. Наставник может оперативно реагировать на отклонения в ходе подготовки, поощрять достижения своего подопечного. Практика показывает, что программы развития молодых сотрудников с высоким потенциалом в сочетании с такой моделью наставничества позволяют более полно раскрыть их способности, а также способствуют уменьшению показателя текучести кадров.

В структурах, входящих в систему Роспотребнадзора, сотрудники, работающие с возбудителями вирусных и бактериальных инфекций, подвергают своё здоровье и даже жизнь опасности. Входящие в эту когорту противочумные учреждения уже более ста лет сталкиваются с потенциальной опасностью заражения сотрудников на рабочем месте, и этот факт нельзя не учитывать, рассматривая богатейший опыт предыдущих поколений.

Показывая в этой статье опыт работы Ростовского-на-Дону противочумного института, нужно отметить повседневный кропотливый труд сотрудников старшего поколения по обучению, передаче навыков работы, мягкому введению в профессию молодёжи, постоянному слежению за неукоснительным соблюдением святая святых «режима», а именно соблюдением требований биологической безопасности работы в лабораториях и отделах института. Такой процесс трудовых будней института существует десятилетиями. В 60–70-е гг., в советский период, обучение молодёжи профессиональным навыкам называли наставничеством. Затем это расхожее слово в некоторой степени было забыто, однако работа в институте всегда шла под эгидой наставничества.

Но всё новое — это хорошо забытое старое, и в последнем десятилетии этот флаг был вновь поднят, и развивается он уже на новом витке практических и теоретических знаний. Федеральной службой по надзору в сфере защиты прав потребителей и благополучия человека был издан Приказ от 12 ноября 2012 г. № 1088 «Об организации наставничества в территориальных органах Роспотребнадзора и подведомственных организациях». Это дало толчок к серьёзному осмыслению и более детальной проработке процессов обучения молодёжи и всех вновь поступающих в институт сотрудников без изменения сути происходящего повседневно. Во исполнение Приказа Роспотребнадзора в институте было разработано Положение о наставничестве, также созданы формы планирования, отчётности и анкетирования. Вся деятельность института по наставничеству осуществляется на основании приказов директора.

Наставничество — это прерогатива наиболее подготовленных сотрудников, имеющих значительный опыт работы, обладающих высокими профессиональными и

моральными качествами, проявляющих способности к воспитательной работе и пользующихся авторитетом в коллективе. Подбор наставника осуществляется руководителем структурного подразделения совместно с администрацией института и зависит от целого ряда факторов, таких как потребности наставляемого, его начальная подготовка, профессиональные знания, навыки, опыт работы.

Срок наставничества, продолжительность которого зависит от степени профессиональной подготовки наставляемого, устанавливается приказом директора по ходатайству начальника научного отдела. Обязательным условием для закрепления за молодым специалистом наставника является их обоюдное согласие, а также возможность создания необходимых условий для совместной работы наставника и наставляемого. В процессе наставничества огромную роль играет личность наставника, ведь далеко не каждый работник (даже профессионал в своей сфере) может стать наставником. Наставник должен обладать рядом характеристик, такими как желание и возможность делиться своими знаниями, ответственность, отзывчивость, целеустремленность, чувство такта, самоорганизованность [12]. Наставничество — процесс, развивающий и мотивирующий не только начинающих сотрудников института, но и самих наставников.

Наставничество используется в обучении / развитии разных категорий сотрудников (включая будущих сотрудников института!) и с различными целями: со старшеклассниками — в целях профориентации, со студентами-стажёрами — для углубления профессионального образования и подготовки к возможной будущей профессиональной специализации, с новыми сотрудниками — с целью адаптации, ускоренного освоения норм и требований, вхождения в полноценный рабочий режим, с состоявшимися профессионально сотрудниками — для подготовки к развитию управленческой карьеры и переходу на более высокие уровни управления [13].

Такой важный процесс работы, как наставничество в институте осуществляется в отношении трёх категорий работников: в коллективе научных сотрудников (включая студентов-стажёров), среди лаборантов и среди прочих работников института. В связи с данной дифференциацией существуют общие требования к процессу наставничества, требования, связанные с выполнением правил безопасной работы, и требования, касающиеся непосредственно каждой отдельной группы сотрудников института.

Особое внимание уделяется требованиям, связанным с выполнением правил безопасной работы. Для каждой из групп сотрудников объём таких требований разнится. Для сотрудников вспомогательных подразделений, какими являются отдел кадров, бухгалтерия, отдел снабжения и другие, он минимален. Для лаборантов и научных сотрудников, занимающихся непосредственно бактериологической работой, принимающих участие в экспериментальной деятельности подразделений, объём требований максимален. Наставник должен передать свой опыт работы с возбудителями особо опасных инфекций. Этому способствуют Санитарные Правила 1.3.3118-13 «Безопасность работы с микроорганизмами I–II групп патогенности (опасности)», которые несколько раз переиздавались в связи с появлением новых знаний и правил в практической работе с возбудителями особо опасных инфекций. Санитарные правила — достаточно объёмный документ, изложенный строгим, официальным языком, но в нём содержится богатый жизненный и профессиональный опыт. Этот документ написан «кровью» наших предшественников, начинавших работать с возбудителями особо опасных инфекций без должного опыта, на ощупь. В начале пути было много ошибок, приводивших к смертельным исходам. Постепенно этот путь был пройден, он многому научил, и теперь задача наставника — передать все свои знания, весь свой опыт и научить новичка работе в особо опасных условиях с возбудителями I–II групп патогенности.

Общими принципами наставничества в институте являются ознакомление наставляемого с историей и традициями института; информирование об общих направлениях, целях и задачах деятельности подразделения и института в целом; развитие у наставляемого интереса к профессиональной деятельности, осуществляемой подразделением; оказание помощи наставляемому в изучении требований нормативно-правовых актов, регламентирующих исполнение его должностных обязанностей и их правоприменение; оказание помощи наставляемому в приобретении им необходимых профессиональных навыков и опыта работы; адаптация наставляемого к условиям осуществления трудовой деятельности с соблюдением требований трудовой дисциплины; развитие способности наставляемого самостоятельно, качественно и своевременно исполнять свои должностные обязанности и поддерживать профессиональный уровень, необходимый для их надлежащего исполнения; развитие у наставляемого профессионально значимых качеств личности, таких как требовательность к себе и заинтересованность в результатах труда; развитие ответственного и сознательного отношения к работе; содействие выработке навыков поведения, соответствующих морально-этическим правилам; формирование у наставляемого активной гражданской и жизненной позиции; приобщение наставляемого к общественной жизни института (поисковая работа, культ-массовая работа и т.п.); развитие стремления к созданию в коллективе благоприятного социально-психологического климата; мотивация наставляемого к эффективной и долгосрочной профессиональной деятельности в институте. Деятельность наставника включает также выявление ошибок, допущенных наставляемым при осуществлении им профессиональной служебной деятельности, и содействие в их устранении, демонстрацию и разъяснение наиболее рациональных методов исполнения должностных обязанностей, оказание наставляемому консультативно-методической помощи при его обращении за профессиональным советом.

Одно из главных напрвалений деятельности Ростовского-на-Дону противочумного института, являющегося научной организацией Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека, — развитие науки, направленной на успешное решение вопросов обеспечения защиты населения от неблагоприятных эпидемиологических осложнений. Поэтому первостепенной задачей института является использование опыта старшего поколения для воспита-

ния молодых научных сотрудников, мотивированных на получение новых знаний и стремящихся к инновационному результату в собственных исследованиях. Наставник должен представить своему подопечному богатый научный мир, ввести в научную среду, погрузить в мир знаний, увидеть и использовать молодой научный задор, поддержать индивидуальность и дать направление научных исследований. Молодой специалист должен постепенно овладеть определённым объемом научных знаний, являющихся необходимой основой вступления в профессиональную жизнь, получить специальную дополнительную подготовку, которая позволит развить умение в своей профессии прогнозировать, моделировать, планировать, выстраивать систему доказательств, делать обобщения и применять знание и профессиональные навыки на практике. Таким образом, основной целью и задачей наставничества в институте является обеспечение формирования кадрового состава института из подготовленных компетентных специалистов, понимающих и выполняющих задачи на высоком профессиональном уровне. Эта ответственная работа, требующая повседневного кропотливого труда, терпения и наставника и наставляемого, включает целый ряд этапов адаптации сотрудника к научной работе.

С помощью наставника и под его контролем наставляемый приобретает практические навыки, необходимые для выполнения задач подразделения и обучается приёмам бактериологической, биохимической, генетической работы с непременным соблюдением требований Санитарных Правил 1.3.3118-13 «Безопасность работы с микроорганизмами I–II групп патогенности (опасности)». Наставник знакомит наставляемого с общими научными направлениями, целями и задачами деятельности подразделения и института в целом, даёт рекомендации наставляемому для изучения тематики специальной литературы, оказывает помощь в подготовке к обсуждению изученного материала в подразделении, на заседаниях Совета молодых учёных и общеинститутских конференциях. Наставник помогает наставляемому в определении направления собственных исследований и диссертационной работы, оказывает помощь в разработке плана диссертации и подготовке к сдаче кандидатских экзаменов. С помощью наставника наставляемый осваивает творческий процесс подготовки публикаций, научных докладов и их презентаций, пишет обзор литературы к диссертационной работе и главы собственных исследований диссертации. Наставник разъясняет молодому учёному важность его публикационной активности, необходимость получения учёной степени. С помощью наставника молодой специалист готовится и включается в работу таких структур института, как Специальные противоэпидемические бригады, референс-центр, центр индикации, Совет молодых учёных и другие.

Важнейшую роль в повышении эффективности наставничества играет обобщение и распространение положительного опыта наставнической деятельности, осуществляемое не только внутри института, но и Федеральной службой по надзору в сфере защиты прав потребителей и благополучия человека, посредством ежегодного анализа наставнической работы всех подведомственных организаций. Повышению эффективности наставничества в институте способствует постоянный контроль наставнической деятельности, регулярный анализ результативности наставника и молодого специалиста, а также проведение анкетирования. В установленные сроки наставник и наставляемый предоставляют отчёты о результатах наставничества, кроме того наставник даёт рекомендации по дальнейшему профессиональному развитию работника. Такой мониторинг позволяет своевременно выявлять необходимость коррекции проводимой работы, необходимость повышения квалификации наставников и наставляемых либо необходимость замены наставника. При положительных результатах выполнения индивидуального плана работы наставника администрация института решает вопрос о его поощрении. Важно учитывать, что наставничество осуществляется наставником не исключительно ради денег, в этом деле важнейшую роль играет морально-этическая составляющая процесса. В институте гармонично сочетаются и моральные, и материальные формы поощрения. В качестве материального поощрения локальными нормативными актами установлены выплаты стимулирующего характера. Также для особенно результативных наставников предусмотрено награждение нагрудным Знаком отличия «Наставник молодёжи Ростовского-на-Дону ордена Трудового Красного Знамени научно-исследовательского противочумного института».

Кроме традиционной модели наставничества в нашем институте нашла применение ещё одна модель наставничества — виртуальное наставничество. Использование информационно-коммуникационных технологий, таких как видеоконференции, платформы для дистанционного обучения, онлайн-сервисы социальных сетей и сообществ практиков. Такая работа получила развитие в последние 2–3 года на базе отдела профессиональной переподготовки специалистов [14]. Виртуальное наставничество позволяет использовать больше учебных ресурсов для освоения новых знаний и навыков, обеспечивает постоянное и творческое общение, использование социальных сетей для привлечения других специалистов и получения разнообразной информации, делая программу наставничества доступной для широкого круга сотрудников института и специалистов других учреждений.

Рассматривая события сегодняшнего дня, а именно пандемию коронавирусной инфекции, необходимо показать, как важно иметь в руках знания, опыт и механизмы управления эпидемическими процессами и наработки практического здравоохранения, которые оставили нам наши предшественники в копилке научно-медицинских достижений прошлых лет. Именно благодаря этому в России удалось избежать взрывного характера пандемического процесса, минимизировать человеческие потери.

В этом аспекте важно сказать и о большой работе, проделанной сотрудниками института, а именно эпидемиологического звена, которые на протяжении многих лет постоянно обучали медицинский контингент города Ростова-на-Дону и Ростовской области правилам профессионального поведения в случае эпидемических осложнений, принятию верных решений, использованию средств индивидуальной защиты, правильному применению средств защиты [15, 16]. Эта в своем роде наставническая работа за пределами института по передаче опыта

работы с возбудителями особо опасных инфекций, пригодилась в сложный период борьбы с коронавирусной инфекцией. Возвращаясь к началу статьи, где описаны модели наставничества, эту модель можно назвать групповое наставничество, модель, в которой один наставник работает с группой из 2-х, 4-х, 6-ти подопечных одновременно. Непосредственное общение происходит периодически по заранее утверждённому графику.

Суть института наставничества состоит в том, что оно позволяет сформировать необходимые профессиональные качества для замещения определенной должности, а также выработать у специалистов верную позицию к исполнению возложенных на них должностных обязанностей. Наставничество может быть формальным и неформальным. Насколько формализован процесс наставничества, зависит от целей наставничества, целевой аудитории, культуры организации. Неформальное наставничество похоже на стихийно возникшие отношения между сотрудниками: обучение и передача знаний осуществляются на основе взаимного интереса и существующих взаимоотношений [17]. Различные методы наставничества имеют широкое распространение в зарубежной практике и считаются эффективной кадровой технологией. Дэвид Клаттербак, гуру наставничества, в своей известной книге «Каждый нуждается в наставнике: забота о таланте в вашей организации»[1] рассматривает две модели наставничества. Североамериканская концепция наставничества подразумевает помощь человека, старшего по возрасту или более профессионального, молодому специалисту. Его задача — давать советы и направлять поведение протеже. Такая модель называется «спонсорским наставничеством». В европейской модели непосредственный руководитель не может быть наставником своего подчиненного, но является участником процесса его обучения. Отношения предполагают двустороннее обучение: наставник и ученик учатся друг у друга, и их отношения являются взаимовыгодными. Эта модель — «Развивающее наставничество».

Научно-исследовательская работа по апробированию внедрения наставничества проведена в пилотных федеральных органах власти. Главный вывод заключается в том, что наставничество — важный метод кадровой работы, обеспечивающий скорейшую адаптацию, профессиональное развитие и карьерный рост государственных служащих [18].

Специалисты разных областей знаний активно интересуются развитием процесса наставничества за рубежом. Благодаря изучению российских и зарубежных практик, методов наставничества, опыта российских предприятий-лидеров по использованию наставничества показана необходимость принятия профессионального стандарта в сфере наставничества, а также развития соответствующей нормативно-правовой базы [19]. На примере педагогических колледжей и университетов Франции и Канады раскрываются организационные, содержательные и методические аспекты педагогической практики студентов (будущих педагогов), роль института наставничества, эффективность организации педагогической практики через взаимодействие преподавателей вуза и учителей-наставников [20, 21]. Изучен опыт и основные направления развития института наставничества в британской педагогической науке, где придают значение также индивидуализированным формам обучения, поддержки и сопровождения [22].

В документе «Методология (целевая модель) наставничества обучающихся для организаций, осуществляющих образовательную деятельность по общеобразовательным, дополнительным общеобразовательным и программам среднего профессионального образования, в том числе с применением лучших практик обмена опытом между обучающимися» широко представлен анализ лучших мировых практик наставничества. Показано, что в программах Германии существует 9 этапов наставнической деятельности, следовательно, оценка проводится 9 раз. В британских средних школах наставничество можно разделить на двенадцать различных моделей в рамках двух широких групп: собственно «наставничество» и «программы обучения и трудоустройства». В Израиле — семейное и взаимное наставничество, в США — взаимное и корпоративное. В образовательных организациях стран Азии, во-первых, весьма популярной формой называется партнёрское наставничество по типу «равный — равному», когда наставник является равным по уровню подопечному, но обладает бóльшими знаниями, опытом, которыми и делится с ним. Во-вторых, в азиатских странах существует виртуальное наставничество, когда советы и рекомендации наставника подопечному даются в режиме онлайн. Наставничество в Китае основано на несколько иной логике: наставники, они свои роли, совершенствуют в первую очередь себя, открывая дорогу другому, наставники сами растут, преодолевая вместе с наставляемыми их трудности и препятствия, и прокладывают дороги и тропинки к новым истинам[2].

Особой средой взаимодействия и обучения является медицина. В учреждениях медицинского профиля опыт применения наставничества особенно важен, потому что на кону здоровье и жизнь человека. Важным принципом медицинской этики является «Не навреди», или primum non nocere (дословно — «прежде всего – не навреди»).

В 70-ые гг. прошлого столетия не только во врачебных кругах широко употребляли термин «трудовая династия». В любом контексте это звучало гордо. Анализ стратегий воспроизводства профессиональной династии в медицинской сфере в современном обществе даёт возможность понять общие характеристики профессиональной преемственности врачей, состоящие в активном

[1] Клаттербак Д. Каждый нуждается в наставнике: забота о таланте в вашей организации. Лондон, CIPD, 2006. Доступно по: https://yandex.ru/search/?lr=39&text=Клаттербак%20Д.%20Каждый%20нуждается%20%20в%20%20наставнике%3A%20забота%20о%20талантах%20%20вашей%20%20организации.%20Лондон%2C%20CЫЗВ%2C%202006.&msp=1

[2] Синягина Н.Ю., Березина В.А., Богачева Т.Ю., Пронькина И.Л. и др. Методология (целевая модель) наставничества обучающихся для организаций, осуществляющих образовательную деятельность по общеобразовательным, дополнительным общеобразовательным и программам среднего профессионального образования, в том числе с применением лучших практик обмена опытом между обучающимися. Москва, 2019. Доступно по: http://k-obr.spb.ru/media/content/docs/5701/Целевая_модель._5.12.2019_для_рассылки.pdf

функционировании наставничества [23]. Ничем не заменить опыт наставничества в работе многопрофильной больницы для адаптации молодых сотрудников [24]. Институт наставничества необходим как для помощи в адаптации новым сотрудникам, так и для содействия молодым специалистам в обретении практических навыков, такой вывод сделан при попытке оценить необходимость системы наставничества в медицинских учреждениях города Москвы [25]. Будучи министром здравоохранения, Вероника Скворцова заявила, что движение наставничества в медицине скоро охватит всю страну. Выпускники вузов благодаря первичной аккредитации могут работать в клиниках со студенческой скамьи [26]. На особом счету опыт создания и внедрения системы внутреннего обучения персонала с использованием современных информационных технологий [27]. Наставничество — это решение проблемы оттока молодых специалистов при катастрофическом положении современной медицины с кадрами [28].

Организация работы по развитию практической и психологической помощи молодым научным сотрудникам и лаборантам, а также другим категориям работников с целью ускорения процесса их профессионального роста, развития способности самостоятельно, качественно и ответственно выполнять должностные обязанности является одной из приоритетных задач реализации кадровой политики в научно-исследовательских подразделениях ФКУЗ «Ростовский-на-Дону противочумный институт Роспотребнадзора». Анализ этого вида деятельности позволил понять, что в институте удалось реанимировать приёмы работы наставника 70–80-х гг., обогатив наставничество новыми методами, технологиями, современными задачами, понятиями. Основой остался научный подход и принцип безопасности в лабораторно-практической работе.

Таким образом, подходы к процессу наставничества в каждой стране отличаются друг от друга. Отличаются и программы адаптации по продолжительности, по содержанию, по подходу к новому сотруднику. Следует ориентироваться на опыт зарубежных стран и перенимать положительные и эффективные аспекты. Но нельзя слепо подражать, потому что в России богатый опыт наставничества, достойный уважения и реабилитации. Нет необходимости заменять адаптированные к российской ментальности и проверенные практикой методы зарубежными терминами, применяемыми в другой профессиональной практике, однако это не означает, что организаторам работы с персоналом и специалистам по обучению и развитию не следует изучать зарубежную и отечественную структуры инновационных процессов[1].

Анализируя опыт наставничества в рамках Ростовского-на-Дону противочумного института Роспотребнадзора , необходимо отметить положительные результаты, которые можно обозначить такими позициями, как уменьшение показателя текучести кадров, повышение активности участия новых сотрудников института в общественной жизни коллектива (особенно это видно на опыте работы Совета молодых учёных), улучшение показателя публикационной активности молодых научных сотрудников, активное участие молодёжи в работе научных конференций, настрой на получение инновационных результатов в собственных исследованиях, мотивация на профессиональный рост и активная подготовка к защите диссертаций.

Финансирование. Исследование не имело спонсорской поддержки.

Finansing. *The study did not have sponsorship.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Conflict of interest. *Authors declares no conflict of interest.*

ЛИТЕРАТУРА

1. Невская Л.В., Эсаулова И.А. Система развития инновационного кадрового потенциала предприятий // *Вестник Пермского национального исследовательского политехнического университета. Социально-экономические науки.* - 2013. - № 21. - С. 72-76. eLIBRARY ID: 20860483
2. Шабанов М.А. Роль наставничества в профессиональном становлении молодых педагогов // *Сибирский учитель.* - 2017. - №1 (110). - С. 100-103. eLIBRARY ID: 29009716
3. Сопегина В.Т. О формировании коммуникативной составляющей педагогической компетенции в процессе наставничества // *Образование и наука.* - 2016. - №2 (131). - С. 55-67. DOI: 10.17853/1994-5639-2016-2-55-67
4. Пастухова Л.С., Сорокина-Исполатова Т.В. Наставничество как социально-педагогический ресурс повышения качества подготовки будущих специалистов // *Отечественная и зарубежная педагогика.* - 2013. - № 6(15). - С. 26-31. eLIBRARY ID: 21052701
5. Никитина В.В. Роль наставничества в современном образовании // *Отечественная и зарубежная педагогика.* - 2013. - № 6(15). - С. 50-56. eLIBRARY ID: 21052704

REFERENCES

1. Nevskaya L.V., Esaulova I.A. Sistema razvitiya innovatsionnogo kadrovogo potentsiala predpriyatii. *Vestnik Permskogo natsional'nogo issledovatel'skogo politekhnicheskogo universiteta. Sotsial'no-ekonomicheskie nauki.* 2013;21:72-76. (In Russ.). eLIBRARY ID: 20860483
2. Shabanov M.A. The role of mentoring for professional becoming of young teachers // *Sibirskii uchitel'.* 2017;1(110):100-103 (In Russ.). eLIBRARY ID: 29009716
3. Sopegina V.T. Communication component formation of teachers' competence in the mentoring process. *The Education and science journal.* 2016;(2):55-67. (In Russ.) DOI: 10.17853/1994-5639-2016-2-55-67
4. Pastukhova L.S., Sorokina-Ispolatova T.V. Tutorship as a socio-pedagogical resource of enhancement of future specialists' training. *Otechestvennaya i zarubezhnaya pedagogika.* 2013;6(15):26-31 (In Russ.). eLIBRARY ID: 21052701
5. Nikitina V.V. Role of tutorship in modern education and the necessity for its revival in higher school. *Otechestvennaya i zarubezhnaya pedagogika.* 2013;6(15):50-56 (In Russ.). eLIBRARY ID: 21052704

[1] Панфилова А.П. Наставничество и обучение на рабочем месте: терминологический анализ зарубежных методов // Современные технологии управления. 2016. № 12 (72). Доступно по: https://sovman.ru/article/7202/

6. Барбасова Д.М. Наставничество в современной корпоративной среде // *Молодой учёный.* - 2013. - № 10. - С. 265-268. eLIBRARY ID: 20534753
7. Талалай М.А., Рогоженко А.А., Кобец Е.А. Наставничество как способ адаптации и развития персонала предприятия // *Новое слово в науке: перспективы развития.* - 2015. - № 3. - С. 320-322. eLIBRARY ID: 24039161
8. Курников К.И. Значение наставничества в деятельности организации // *Международный научно-исследовательский журнал.* - 2013. - № 11-2 (18). - С.54-55. eLIBRARY ID: 21069777
9. Белалова Е.А., Лымарёва О.А. Система наставничества как элемент совершенствования развития персонала российских банков // *Экономика устойчивого развития.* - 2016. - № 1(25). - С. 34-37. eLIBRARY ID: 25740936
10. Дыбаль И.И. Наставничество, как основа преемственности традиций, на примере творчества Валериана Алексеевича Сергина // *Актуальные проблемы гуманитарных и естественных наук.* - 2014. - № 2-3. - С. 295-298. eLIBRARY ID: 21494543
11. Эсаулова И.А. Новые модели наставничества в практике обучения и развития персонала зарубежных компаний // *Стратегии бизнеса.* - 2017. - № 6 (38). - С. 8-13. DOI: 10.17747/2311-7184-2017-6-08-13
12. Польникова Е.А. Наставничество как эффективный инструмент управления талантами // *Международный научно-исследовательский журнал.* - 2016. - № 11 (53). Ч. 5. - С. 118-119. DOI: 10.18454/IRJ.2016.53.033
13. Кларин М.В. Современное наставничество: новые черты традиционной практики в организациях XXI века // *ЭТАП: экономическая теория, анализ, практика.* - 2016. - № 5. - С. 92-112. eLIBRARY ID: 27341838
14. Сизова Ю.В., Бурлакова О.С., Водопьянов А.С., Черепахина И.Я., Балахнова В.В.,и др. Возможность использования дистанционных технологий при подготовке специалистов по особо опасным инфекциям // *Здоровье населения и среда обитания.* - 2017. - № 7. - С. 11-17. DOI: 10.35627/2219-5238/2017-292-7-11-13
15. Пичурина Н.Л., Бурлакова О.С., Водяницкая С.Ю., Сизова Ю.В., Чемисова О.С., Титова С.В. Консультативные семинары как форма повышения профессиональной компетенции специалистов Роспотребнадзора и министерства здравоохранения Ростовской области в период подготовки к проведению Чемпионата мира по футболу 2018 в городе Ростове-на-Дону // *Социально-значимые и особо опасные инфекционные заболевания: Материалы V Всероссийской междисциплинарной научно-практической конференции с международным участием.* - Сочи. 2018. С. 189-191. eLIBRARY ID: 37636443
16. Рыжова А.А., Водяницкая С.Ю., Баташев В.В. Опыт работы по повышению уровня профессиональной компетенции специалистов в области профилактики ООИ среди различных групп населения в период подготовки и проведения массовых мероприятий с международным участием // *Устойчивое развитие науки и образования.* - 2018. - № 5. - С. 122-127. eLIBRARY ID: 35177564
17. Савенко А. А., Трофимова Т.В. Технология наставничества на государственной гражданской службе // *Молодой ученый.* - 2019. - № 23 (261). - С. 294-296. eLIBRARY ID: 38191602
18. Клищ Н.Н., Январев В.А. *Наставничество на государственной службе – новая технология профессионального развития государственных служащих (зарубежный и российский опыт наставничества на государственной службе):* Препринт WP8/2014/01. Нац. исслед. ун-т «Высшая школа экономики». – М.: Изд. дом Высшей школы экономики, 2014. 64 с.

6. Barbasova D.M. Nastavnichestvo v sovremennoi korporativnoi srede. *Molodoi uchenyi.* 2013;10:265-268 (In Russ.). eLIBRARY ID: 20534753
7. Talalai M.A., Rogozhenko A.A., Kobets E.A. Nastavnichestvo kak sposob adaptatsii i razvitiya personala predpriyatiya. *Novoe slovo v nauke: perspektivy razvitiya.* 2015;(3):320-322 (In Russ.). eLIBRARY ID: 24039161
8. Kurnikov K.I. The value of tutorship in the organization. *Mezhdunarodnyi nauchno-issledovatel'skii zhurnal.* 2013;11-2(18):54-55 (In Russ.). eLIBRARY ID: 21069777
9. Belalova E.A., Lymareva O.A. Mentoring system as a part of improvement of staff of russian banks. *Ekonomika ustoichivogo razvitiya.* 2016;1(25):34-37 (In Russ.). eLIBRARY ID: 25740936
10. Dybal' I.I. Nastavnichestvo, kak osnova preemstvennosti traditsii, na primere tvorchestva Valeriana Alekseevicha Sergina. *Aktual'nye problemy gumanitarnykh i estestvennykh nauk.* 2014;2-3:295-298 (In Russ.). eLIBRARY ID: 21494543
11. Esaulova I.A. New mentoring models in the foreign companies practices of personnel learning and development. *Business Strategies.* 2017;(6):08-13. (In Russ.) DOI: 10.17747/2311-7184-2017-6-08-13
12. Pol'nikova E.A. Mentoring as an effective tool talent management. *Mezhdunarodnyi nauchno-issledovatel'skii zhurnal.* 2016;11(53):118-119 (In Russ.). DOI: 10.18454/IRJ.2016.53.033
13. Klarin M.V. Modern mentoring: the new features of the traditional practices in organizations of the XXI century. *ETAP: ekonomicheskaya teoriya, analiz, praktika.* 2016;5:92-112 (In Russ.). eLIBRARY ID: 27341838
14. Sizova Yu.V., Burlakova O.S., Vodop'yanov A.S., Cherepakhina I.Ya., Balakhnova V.V. et al. Possibility of use of distance technologies in training on especially dangerous infections. *Zdorov'e naseleniya i sreda obitaniya.* 2017;7:11-17 (In Russ.). DOI: 10.35627/2219-5238/2017-292-7-11-13
15. Pichurina N.L., Burlakova O.S., Vodyanitskaya S.Yu., Sizova U.V., Chemisova O.S., Titova S.V. Konsul'tativnye seminary kak forma povysheniya professional'noi kompetentsii spetsialistov Rospotrebnadzora i ministerstva zdravookhraneniya Rostovskoi oblasti v period podgotovki k provedeniyu Chempionata mira po futbolu 2018 v gorode Rostove-na-Donu. *Sotsial'no-znachimye i osobo opasnye infektsionnye zabolevaniya: Materialy V Vserossiiskoi mezhdistsiplinarnoi nauchno-prakticheskoi konferentsii s mezhdunarodnym uchastiem.* Sochi; 2018:189-191 (In Russ.). eLIBRARY ID: 37636443
16. Ryzhova A.A., Vodyanitskaya S.Yu., Batashev V.V. Experience to raise the level of specialists professional competence in the field of dangerous diseases prevention among different groups in the period of preparation and holding mass events with international participation. *Ustoichivoe razvitie nauki i obrazovaniya.* 2018;5:122-127 (In Russ.). eLIBRARY ID: 35177564
17. Savenko A.A., Trofimova T.V. Tekhnologiya nastavnichestva na gosudarstvennoj grazhdanskoj sluzhbe. *Molodoj uchenyj.* 2019;23(261):294-296. eLIBRARY ID: 38191602
18. Klishch N.N., Yanvarev V.A. *Nastavnichestvo na gosudarstvennoi sluzhbe – novaya tekhnologiya professional'nogo razvitiya gosudarstvennykh sluzhashchikh (zarubezhnyi i rossiiskii opyt nastavnichestva na gosudarstvennoi sluzhbe):* Preprint WP8/2014/01. Nats. issled. un-t «Vysshaya shkola ekonomiki». M.: Izd. dom Vysshei shkoly ekonomiki, 2014. 64 c. (In Russ.).
19. Loktyukhina N.V., Nazarova U.A., Shabaeva S.V. Mentoring system development: russian and foreign experience. *Nepreryvnoe obrazovanie: XXI vek.* 2019;4(28):136-151 (In Russ.). DOI: 10.15393/j5.art.2019.5155
20. Kapranova V.A., Demidovich M.I. Organizatsiya pedagogicheskoi praktiki budushchikh uchitelei: zarubezhnyi opyt.

19. Локтюхина Н.В., Назарова У.А., Шабаева С.В. Развитие системы наставничества: российский и зарубежный опыт // *Непрерывное образование: XXI век.* - 2019. - № 4(28). - С. 136-151. DOI: 10.15393/j5.art.2019.5155
20. Капранова В.А., Демидович М.И. Организация педагогической практики будущих учителей: зарубежный опыт // *Весці БДПУ. Серыя 1. Педагогіка. Псіхалогія. Філалогія.* - 2012. - № 1(71). - С.3-6. eLIBRARY ID: 41142073
21. Лучкина Т.В. Особенности содействия профессиональному становлению начинающего учителя в Канаде // *Известия Российского государственного педагогического университета им. А.И. Герцена.* - 2009. - № 112. - С. 36-45. eLIBRARY ID: 12809693
22. Дудина Е.А. Содержание наставничества в системе непрерывного профессионального развития педагогических кадров в Великобритании // *Вестник Новосибирского государственного педагогического университета.* - 2017.- Т.7. № 1. - С. 49-62. DOI: 10.15293/2226-3365.1701.04
23. Нор-Аревян О.А. Стратегии воспроизводства профессиональной медицинской династии // *Гуманитарий Юга России.* - 2020. - Т.9. № 4. - С.62-72. DOI: 10.18522/2227-8656.2020.4.5
24. Богуш Е.А., Радулова Н.А. Система адаптации и наставничества в многопрофильной больнице // *Аспирантский вестник Поволжья.* - 2015. - № 1-2. - С. 215-221. eLIBRARY ID: 23917665
25. Бурдастова Ю.В. Наставничество в системе здравоохранения: тренд или необходимость? // *Народонаселение.* - 2020. - Т. 23. № 1. - С. 148-154. DOI: 10.19181/population.2020.23.1.12
26. Богатырева Г. Как организовать наставничество в клинике. Практические рекомендации // *Здравоохранение.* - 2018. - № 5. - С.68-81. eLIBRARY ID: 36737817
27. Чурекова И.О., Горшков А.А. Построение системы внутреннего обучения персонала в медицинской организации // *Менеджмент качества в медицине.* - 2019. - №3. - С. 108-113. eLIBRARY ID: 41173270
28. Некрасова О.А., Шепель Л.И. Наставничество в современной медицине // *Медсестра.* - 2019. - № 6. - С. 60-62. eLIBRARY ID: 37789257

Vestsi BDPU. Seryya 1. Pedagogika. Psikhalogiya. Filalogiya. 2012;1(71):3-6 (In Russ.). eLIBRARY ID: 41142073
21. Luchkina T.V. Characteristic features of supporting new teacher professional development in Canada. *Izvestiya Rossiiskogo gosudarstvennogo pedagogicheskogo universiteta im. A.I. Gertsena.* 2009;112:36-45. (in Russ.). eLIBRARY ID: 12809693
22. Dudina E. A. The essence of mentoring in continuing professional development of teaching staff in Great Britain. *Novosibirsk State Pedagogical University Bulletin.* 2017;7(1):49–62. DOI: 10.15293/2226-3365.1701.04
23. Nor-Arevyan O.A. Strategies for Professional Medical Dynasty Reproduction. *Humanities of the South of Russia.* 2020;9(4):62-72. (In Russ.). DOI: 10.18522/2227-8656.2020.4.5
24. Bogush E.A., Radulova N.A. Adaptation and mentoring in a general hospital. *Aspirantskii vestnik Povolzh'ya.* 2015;1-2:215-221 (In Russ.). eLIBRARY ID: 23917665
25. Burdastova Y.V. Mentoring in healthcare: trend or necessity? *Population.* 2020;23(1):148-154. (In Russ.). DOI: 10.19181/population.2020.23.1.12
26. Bogatyreva G. Kak organizovat' nastavnichestvo v klinike. *Prakticheskie rekomendatsii. Zdravookhranenie.* 2018;5:68-81 (In Russ.). eLIBRARY ID: 36737817
27. Churekova I.O., Gorshkov A.A. Building a system of continuous internal training in a medical organization. *Menedzhment kachestva v meditsine.* 2019;3:108-113 (In Russ.). eLIBRARY ID: 41173270
28. Nekrasova O.A., Shepel' L.I. Mentoring in modern medicine. *Medsestra.*2019;6:60-62 (In Russ.). eLIBRARY ID: 37789257

Информация об авторах

Щипелева Ирина Александровна, к.б.н., исполняющий обязанности начальника научного отдела, учёный секретарь, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID: 0000-0001-6263-8155. E-mail: shipeleva.irina@yandex.ru.

Марковская Елена Ивановна, к.м.н., старший научный сотрудник, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID: 0000-0002-5360-951X. E-mail: markovskay2014@yndex.ru

Кретенчук Оксана Фёдоровна, к.б.н., старший научный сотрудник, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID: 0000-0001-5299-0243. E-mail: oksidjinf@mail.ru

Чемисова Ольга Сергеевна, к.б.н., исполняющий обязанности заведующего музеем живых культур с центром патогенных для человека вибрионов, Ростовский-на-Дону противочумный институт Роспотребнадзора, Ростов-на-Дону, Россия. ORCID: 0000-0002-4059-2879. E-mail: chemisova@inbox.ru

Information about the authors

Irina A. Shepeleva, Cand. Sci. (Bio.), acting head of the academic Department, academic Secretary, Rostov-on-Don anti-plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID: 0000-0001-6263-8155. e-mail: shipeleva.irina@yandex.ru.

Elena I. Markovskaya, Cand. Sci. (Med.), Senior Researcher, Rostov-on-Don anti-plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID: 0000-0002-5360-951X. e-mail: markovskay2014@yndex.ru.

Oksana F. Kretenchuk, Cand. Sci. (Bio.), senior researcher, Rostov-on-Don anti-plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID: 0000-0001-5299-0243. E-mail: oksidjinf@mail.ru.

Olga S. Chemisova, Cand. Sci. (Bio.), Acting Head of the Museum of Living Cultures with the Center for Vibrions pathogenic to humans, Rostov-on-Don anti-plague Institute of Rospotrebnadzor, Rostov-on-Don, Russia. ORCID: 0000-0002-4059-2879. e-mail: chemisova@inbox.ru.

Вклад авторов

Щипелева Ирина Александровна — концепция и анализ материала;

Марковская Елена Ивановна — сбор материала и написание статьи;

Чемисова Ольга Сергеевна — обзор публикаций по теме статьи;

Кретенчук Оксана Фёдоровна — структурирование и обработка материала;

Ответственность за финальную версию статьи — все соавторы.

Authors contribution

Irina A. Shchipeleva — conception and analysis of the material;

Elena I. Markovskaya — collecting material and writing an article;

Olga S. Chemisova — review of publications on the topic of the article;

Oksana F. Kretenchuk — structuring and processing of the material;

All co-authors are responsible for the final version of the article.

Получено / Recived: 19.02.2021
Принято к печати / Accepted: 26.02.2021

УДК: 618.1
DOI DOI 10.21886/2219-8075-2021-12-1-98-104

История Ростовской школы акушерства и гинекологии (к празднованию 90-летия Ростовского государственного медицинского университета)

А.Ф. Михельсон, Ю.Ю. Чеботарева, Е.П. Евдокимова

Ростовский государственный медицинский университет, Ростов-на-Дону, Россия

В ноябре 1915 года в г. Ростове-на-Дону появился Варшавский университет, впоследствии ставший Донским университетом, а в настоящее время являющийся Ростовским государственным медицинским университетом. Кафедра и клиника акушерства и женских болезней в Ростове-на-Дону были организованы в составе медицинского факультета Варшавского университета, эвакуированного в Ростов-на-Дону также в 1915 г. Родоначальником кафедры стал доктор медицины, профессор Анастасий Александрович Сицинский. С его деятельности начинается Ростовская школа акушеров-гинекологов, которая отличается преемственностью, наличием семейных династий, соблюдением традиций в передаче знаний, навыков, нравственных качеств. Представленные в статье этапы развития Ростовской школы акушерства и гинекологии имеют актуальное значение в аспекте изучения проблем, связанных с историей медицины. С целью анализа научных направлений Ростовской школы акушерства и гинекологии были изучены особенности работы кафедр акушерства и гинекологии Ростовского государственного медицинского университета. Проведена оценка преемственности в научной работе и практической деятельности.

В статье представлены особенности развития Ростовской школы акушерства и гинекологии за последние 90 лет. Проведен анализ работы отдельных кафедр акушерства и гинекологии, их научных направлений.

Ключевые слова: ростовская школа акушеров-гинекологов.

Для цитирования: Михельсон А.Ф., Чеботарева Ю.Ю., Евдокимова Е.П. История Ростовской школы акушерства и гинекологии (к празднованию 90-летия Ростовского государственного медицинского университета). *Медицинский вестник Юга России.* 2021;12(1):98-104. DOI 10.21886/2219-8075-2021-12-1-98-104.

Контактное лицо: Чеботарева Юлия Юрьевна, chebotarevajulia@inbox.ru.

History of the Rostov school of obstetrics and gynecology (to celebrate the 90th anniversary of the Rostov State Medical University, Ministry of Health of Russia)

A.F. Mikhelson, Yu.Yu. Chebotareva, E.P. Evdokimova

Rostov State Medical University, Rostov-on-Don, Russia

In November 1915, the Russian University of Warsaw appeared in Rostov-on-Don, which later became the Donskoy University, and in the present – the Rostov State Medical University. The Department and clinic of obstetrics and women's diseases in Rostov-on-Don were set up as part of the medical department of the University of Warsaw, which was evacuated to Rostov-on-Don also in 1915. The founder of the Department was a doctor of medicine, Professor Anastasiy Alexandrovich Sitcinski. The Rostov school of obstetricians and gynecologists, which is distinguished by continuity, the presence of family dynasties, observance of traditions in the transfer of knowledge, skills, and moral qualities, began with the activities of this doctor. The stages of development of the Rostov school of obstetrics and gynecology presented in the article are of current importance in the aspect of studying problems related to the history of medicine. In order to analyze the scientific directions of the Rostov school of obstetrics and gynecology, the peculiarities of the work of the departments of obstetrics and gynecology of the Rostov state medical University were studied. The assessment of continuity in scientific work and practical activities were carried out. The article presents the features of the development of the Rostov school of obstetrics and gynecology over the past 90 years. The work of individual departments of obstetrics and gynecology, their scientific directions were analyzed.

Keywords: Rostov school of obstetrics and gynecology.

For citation: Mikhelson A.F., Chebotareva Yu.Yu., Evdokimova E.P. History of the Rostov school of obstetrics and gynecology (to celebrate the 90th anniversary of the Rostov State Medical University, Ministry of Health of Russia). *Medical Herald of the South of Russia.* 2021;12(1):98-104. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-98-104.

Corresponding author: Chebotareva Yulia, chebotarevajulia@inbox.ru.

А.Ф. Михельсон, Ю.Ю. Чеботарева, Е.П. Евдокимова

ИСТОРИЯ РОСТОВСКОЙ ШКОЛЫ АКУШЕРСТВА И ГИНЕКОЛОГИИ (К ПРАЗДНОВАНИЮ 90-ЛЕТИЯ РОСТОВСКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА)

10 октября 2020 г. исполнилось 90 лет с того момента, как Женский медицинский институт вошёл в состав Медицинского факультета Северо-Кавказского университета, и, согласно распоряжению Наркомпроса и постановлению ЦИК и СНК СССР, был основан Ростовский медицинский институт. Ростовский государственный медицинский университет — одно из старейших учебных заведений нашей страны. В ноябре 1915 г., в период Первой мировой войны в Ростов-на-Дону был эвакуирован Варшавский университет, ставший впоследствии Донским университетом. В 1925 г. Донской университет был переименован в Северо-Кавказский государственный университет. С 1965 г. институт приобретает статус союзного подчинения и становится Ростовским государственным медицинским институтом. В послевоенные годы большой вклад в развитие науки, обучение и воспитание студентов внесли заслуженные деятели науки профессора Н.В. Данилов, П.А. Соколов, Е.М. Губарев, В.А. Никольский, А.Н. Гордиенко, А.Р. Ханамиров, П.П. Коваленко, П.Я. Лельчук, А.А. Колосова, Е.К. Алимова, В.И. Русаков, кавалер ордена Ленина проф. Т.Д. Янович и многие другие. В 1980 г. за заслуги в деле подготовки кадров медицинский институт был награжден орденом Дружбы народов [1].

Кафедра и клиника акушерства и женских болезней в Ростове-на-Дону были организованы в составе медицинского факультета Варшавского университета. Родоначальником кафедры стал доктор медицины, профессор Анастасий Александрович Сицинский [1, 2]. С его деятельности начинается Ростовская школа акушеров-гинекологов, которую отличают преемственность, стремление к развитию приоритетных научных направлений, соблюдение врачебных традиций в передаче знаний, навыков, нравственных качеств.

Учитывая все вышеизложенное, этапы формирования школы акушерства и гинекологии имеют актуальное значение в аспекте изучения проблем, связанных с историей медицины. Целью исследования стало проанализировать этапы развития ростовской школы акушерства и гинекологии путем изучения исторического наследия.

Изучены труды основоположников акушерско-гинекологической службы в Ростовской области. Проведена оценка преемственности в научных работах.

История возникновения кафедры и клиники «акушерства и женских болезней» в Ростове-на-Дону берёт свое начало с конца 1915 г., когда она была создана в составе медицинского факультета Варшавского университета, эвакуированного в Ростов-на-Дону в разгар Первой мировой войны. Возглавил её доктор медицины, проф. А.А. Сицинский, которого считают учеником выдающегося российского и советского акушера-гинеколога Дмитрия Оскаровича Отта. Имя последнего носит Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта» в Санкт-Петербурге. Нами обнаружен бумажный вариант публикации «Лечение заразных послеродовых заболеваний в полости матки», изданной в 1904, в Санкт-Петербурге [3]. Автор — доктор медицины А.А. Сицинский, ассистент клинического повивального гинекологического института и акушер дворцового госпиталя в Санкт-Петербурге. Предисловие написано профессором Д.О. Оттом. Анастасий Александрович с 1909 г. заведовал кафедрой акушерства и женских болезней Женского медицинского института, с 1914 г. — кафедрой Варшавского университета. После эвакуации в 1915 г. под руководством А.А. Сицинского были организованы кафедра и клиника акушерства и женских болезней Донского университета, научными направлениями которой стали лечение послеродовых осложнений и пластическая хирургия. Клиника становится местом возникновения Ростовской школы акушеров-гинекологов, однако её основателем считают доктора медицинских наук, профессора Соловьёва Федора Алексеевича [4].

По данным литературы, Федор Алексеевич родился в 1879 г. в семье учителя, по окончании Харьковского университета он стал научным сотрудником, защитил в 1908 г. диссертацию и повышал знания по акушерству и гинекологии в Германии и Австрии, в клиниках Берлина, Дрездена, Вены [4]. В 1911 г. Ф.А. Соловьёв стал приват доцентом кафедры акушерства и гинекологии Харьковского университета и заведующим повивальной школы. В период гражданской войны Федор Алексеевич работал секретарем профессионального союза военных врачей, председателем младших преподавателей медфака Харьковского университета, а в 1919 г. выехал в Ростов-на-Дону, где в то время находилась его семья. Ф.А. Соловьёв читал лекции в Ростовском городском женском медицинском институте, а после смерти Сицинского Соловьёва избирают заведующим кафедрой. Он укрепляет кафедру и клинику врачебными, научно-педагогическими и лаборантскими кадрами. Научными направлениями кафедры становятся оперативная гинекология, гинекологическая эндокринология, многоплодная беременность. Учениками профессора Соловьёва считают Петра Ильича Силина, Гавриила Климентьевича Черепахина, Николая Васильевича Крупенникова, Людвига Борисовича Теодора, Петра Яковлевича Лельчука, благодаря которым формировалась научная школа, где прослеживалась преемственность поколений и передача накопленного опыта [4]. Благодаря слаженной работе кафедры были изучены процессы, раскрывающие эндокринные механизмы гинекологических заболеваний, что отражено в следующих публикациях: «О гипофизарной терапии в гинекологии», «Схема взаимоотношений яичников с другими железами внутренней секреции». Написаны монографии «Однояйцовые близнецы», «Электротерапия в гинекологии», «Подготовка больных к операции» [4]. В 1922 г. Ф.А. Соловьев организовал журнал «Медицинская мысль» и стал его редактором. В редакционный совет входили профессора Н.А. Богораз, П.В. Никольский, П.И. Эмдин, К.Х. Орлов, А.И. Ющенко, В.П. Вознесенский и др. Проф. Ф.А. Соловьёв также активно работал и в других изданиях, являясь редактором отдела охраны материнства и младенчества журналов «Советская медицина Северного Кавказа», «Акушерство и женские болезни», «Медицинское обозрение Нижнего Поволжья» и др. Написал два раздела в фундаментальном руководстве по гинекологии (под редакцией Л.А. Кривского) [5].

На кафедре большое внимание уделялось лечебной работе. Разрабатывалось оперативное лечение гинекологических свищей, были сконструированы самодержащи-

еся инструменты для пластических операций на влагалище и промежности.

Через школу Федора Алексеевича прошли сотни врачей, получивших высокие квалификации, целый ряд учеников-последователей. Г.К. Черепахин стал заведующим кафедрой в Горьковском мединституте, И.В. Крупенников, возглавил отдел НИИ курортологии в Кисловодске. Людвиг Борисович Теодор с 1932 г. заведовал кафедрой акушерства и гинекологии педиатрического факультета Ростовского-на-Дону медицинского института [2, 4]. В начале Великой Отечественной войны проф. Людвиг Борисович служил начальником хирургического отделения эвакогоспиталя, затем был переведен заведующим кафедрой акушерства 4-го Московского мединститута (1942–1943 гг.), а в 1943–1946 гг. работал заведующим кафедрой такой же клиники в Астраханском мединституте. Одновременно — главный врач областного Астраханского онкодиспансера, который сам организовал и оснастил радием и рентгеном, главный онколог и акушер-гинеколог Астраханской области. С 1945 по 1948 гг. Людвиг Борисович руководил гинекологическим отделением Ростовского научно-исследовательского онкологического института. С 1948 по 1963 гг. заведовал кафедрой акушерства и гинекологии Черновицкого мединститута [2, 4].

Новый виток в истории развития акушерства и гинекологии в Ростове-на-Дону связан с учеником Ф.А. Соловьёва профессором Петром Яковлевичем Лельчуком, который в 1934 г. стал заведующим кафедрой акушерства и гинекологии Ростовского медицинского института и по праву считается патриархом Ростовской школы акушеров-гинекологов [6].

П.Я. Лельчук родился 1898 г. в г. Ростове-на-Дону, в 1916 г. окончил мужскую гимназию, в 1922 г. — медицинский факультет Донского университета, в 1935 г. по совокупности научных работ ему присвоена ученая степень кандидата медицинских наук и он защитил докторскую диссертацию [2, 4, 6]. В марте 1937 г. утверждён в степени доктора, а в апреле 1938 г. — в учёном звании профессора. На кафедре продолжили научное направление, заложенное А.Ф. Соловьевым, связанное с изучением механизмов развития эндокринных гинекологических заболеваний. Приоритетными стали исследования в области детской и подростковой гинекологии, выполненные ученицами Петра Яковлевича В.П. Юровской, Л.Я. Блуштейн, А.С. Заводовой. В 1956 г. на базе РНИИАП было создано первое, единственное на Северном Кавказе, отделение гинекологии детского возраста, где по распоряжению Минздрава проводилась подготовка специалистов — детских гинекологов — из педиатров в клинической ординатуре.

Научные исследования кафедры были связаны с изучением дисфункциональных маточных кровотечений, бесплодия, аменореи, синдрома склерополикистозных яичников, миомы матки [7, 8].

Решались научные вопросы, связанные с трансплантацией ткани эндометрия и яичников в условиях эксперимента на животных. Необходимость по возможности бережной, щадящей терапии неполноценно функционирующих яичников привела к попытке пересадки их ткани. Ученик П.Я. Лельчука, доцент А. М. Килимник разработал метод проточного капельного консервирования ткани яичников, который с успехом применяется не только в гинекологии, но и при консервации тканей в хирургии [7]. Материалы этих исследований нашли свое отражение в монографии «Репродуктивная функция в онтогенезе человека», ответственным редактором которой был П. Я. Лельчук [9]. Хотелось бы отметить самого главного помощника Петра Яковлевича — старшего лаборанта Садовниченко А.И. Анна Ивановна выполняла все необходимые методики экспериментального исследования, включая проведение тогда инновационных гормональных методик.

Кроме того, научные направления кафедры были направлены на изучение туберкулеза половых органов (к.м.н. Ведерман Нина Ашатовна), опухолей матки и яичников. Кафедра занималась изучением профилактики гинекологической заболеваемости, включая массовые профилактические осмотры женщин, работающих на промышленных предприятиях, обозначен вектор в работе женской консультации [10, 11]. С приходом нового поколения исследователей на кафедре начали интенсивно разрабатываться вопросы перинатальной охраны плода. В работах Н.В. Рымашевского и В.И. Орлова были представлены данные по регуляции сердечной деятельности плода и новые взгляды на патогенез и принципы лечения преждевременных родов.

Петр Яковлевич Лельчук был автором 120 научных работ, в том числе 2-х монографий, 2-х глав в многотомном руководстве «Акушерство и гинекология», 2-х глав в пособии для участковых врачей, 5-ти научно-популярных брошюр и ряда методических рекомендаций. Под его руководством издано 7 сборников научных трудов, научно-популярная книга «Мать и ребенок», ряд научно-популярных брошюр [6]. П. Я. Лельчук — член правления и почетный член Всесоюзного и Всероссийского научных обществ акушеров-гинекологов, Почетный председатель и председатель научного общества акушеров-гинекологов Ростовской области, редактор раздела «Акушерство и гинекология» в Большой Медицинской Энциклопедии, член редакционной коллегии журнала «Акушерство и гинекология», член комиссии родовспоможения НКЗдрава РСФСР, участник пяти Международных конгрессов, депутат Ростовского Городского Совета депутатов трудящихся II и III созывов. П. Я. Лельчук — отличник здравоохранения, награжден Орденом «Знак Почета» и десятью медалями [6].

В клинике выполнялись в полном объёме все гинекологические операции. Сам Петр Яковлевич был прекрасным хирургом и стоял за операционным столом до 80 лет. Свое мастерство передал таким корифеям ростовской школы акушеров-гинекологов как Э.А. Ковалева, Л.Д. Людмирская, Т.Н. Денисенко, Е.П. Евдокимова. Огромное внимание Петр Яковлевич уделял повышению квалификации врачей, на протяжении десятков лет возглавляя Областную комиссию по родовспоможению. Считают, что Петром Яковлевичем создана школа акушеров-гинекологов Северного Кавказа, поскольку под его руководством выполнено более 300 научных работ, в том числе 15 докторских и 45 кандидатских диссертаций [2, 4, 6]. Среди учеников Петра Яковлевича — три директора НИИ, девять заведующих кафедрами, пять доцентов, пять старших научных сотрудников. Заслуженный деятель науки РСФСР П.Я. Лельчук является одним из

организаторов и руководителей НИИ акушерства и педиатрии г. Ростов-на-Дону. П.Я. Лельчук руководил кафедрой в течение 43 лет (1936–1979 гг.), на 90-м году жизни ушел на пенсию [2, 4].

Новый этап начался с 1985 г., когда кафедру возглавил проф. Николай Владимирович Рымашевский. Он руководил ею в течение 18 лет. За эти годы на кафедре разработаны уникальные научные направления по проблемам перинатологии, оперативной гинекологии, транссексуализма, менопаузальной гормональной терапии [2, 4]. Рымашевский родился 1 января 1945 г. в Ростове-на-Дону в семье врачей. В 1969 г. окончил Ростовский государственный медицинский институт. В 1971 г. — клиническую ординатуру на кафедре акушерства и гинекологии, поступил в аспирантуру. В 1974 г. защитил кандидатскую диссертацию. С 1974–1984 гг. работал ассистентом кафедры акушерства и гинекологии. В 1985 г. защитил докторскую диссертацию и в этом же году был избран заведующим кафедрой акушерства и гинекологии. В 1986 г. — утверждён в ученом звании профессора. На кафедре первыми в Ростовской области начали заниматься разработкой и внедрением основ перинатальной медицины, включая ультразвуковые, допплерометрические и кардиотокографические методы диагностики в акушерстве и гинекологии. У истоков стояли проф. А.Ф. Михельсон, доц. А.А. Окороков, А.Е. Волков. Проф. И.О. Буштырева внесла большой вклад в изучение менопаузальной гормональной терапии. Под руководством заслуженного врача РФ, проф. Н.В. Рымашевского защищены 2 докторские и 28 кандидатских диссертаций, выпущены в свет 4 монографии, разработан ряд новых методов диагностики, лечения и оперативных вмешательств, которые защищены патентами. Николай Владимирович — автор более 120 научных работ. Под его руководством коллектив кафедры неоднократно получал гранды от фармацевтических компаний и общественных фондов за лучшие проекты научных исследований, результаты которых получали высокую оценку на съездах акушеров-гинекологов России, а также международных симпозиумах.

В 2002 г. кафедру возглавил д.м.н., проф. Владимир Иванович Орлов. Одновременно, с 1983 г. проф. В.И. Орлов являлся директором Ростовского научно-исследовательского института акушерства и педиатрии МЗ РФ. В 1988 г. он успешно защитил докторскую диссертацию на тему: «Клинико-экспериментальное обоснование диагностики и немедикаментозной терапии некоторых форм невынашивания беременности». В 1991 г. ему присвоено звание профессора.

Научные интересы профессора В.И. Орлова охватывали широкий круг наиболее актуальных проблем акушерства, гинекологии и перинатальной медицины. Под его руководством проведены многолетние фундаментальные исследования, связанные с изучением теоретических и практических аспектов патологии репродукции. Впервые в мировой практике профессором В.И. Орловым установлены механизмы формирования гестационной доминанты, а также существование 3-х типов функциональной системы «мать-плацента-плод», с достоверными различиями в течение беременности, родов и перинатальными исходами. Его фундаментальные научные исследования легли в основу разработки принципиально новой концепции невынашивания беременности, позволили разработать безмедикаментозные методы, улучшающие маточно-плацентарный кровоток. Профессором В.И. Орловым впервые установлена роль морфо-функциональных асимметрий и биоритмологических особенностей женской репродуктивной системы в оптимизации экстракорпорального оплодотворения и искусственной инсеминации. Под его руководством выдвинута и экспериментально обоснована новая концепция о роли плода в инициации родовой деятельности. Он развернул широкие исследования по изучению интегративных связей в гемодинамической подсистеме «мать-плацента-плод» и поиску путей оптимизации маточного и пуповинного кровотока. Проф. В.И. Орлов — член Правления Российской ассоциации акушеров-гинекологов, член Европейской ассоциации акушеров-гинекологов, член редакционной коллегии журналов «Акушерство и гинекология», «Вестник Российской ассоциации акушеров-гинекологов». За изобретательскую работу удостоен звания «Заслуженный изобретатель России». Награжден орденом «За заслуги перед Отечеством» IV степени, орденом «Знак Почета», медалью «За доблестный труд». С 1983 г. в Ростовском НИИ акушерства и педиатрии Минздрава России под руководством проф. В.И. Орлова созданы лаборатория физиологии и перинатальной охраны плода, лаборатория иммуноферментного анализа, использующая новейшие разработки биотехнологий, организован Центр репродукции человека и экстракорпорального оплодотворения. Научная и изобретательская деятельность помогла В.И. Орлову создать свою научную школу, ученикам которой он передавал богатый опыт и знания блестящего клинициста, диагноста, талантливого хирурга и ученого. Под его руководством защищены и выполнены 22 кандидатских и 4 докторских диссертации, опубликованы 200 научных работ, 34 изобретения, 3 монографии, 1 справочник и 28 методических рекомендаций.

В настоящее время кафедру возглавляет профессор Александр Николаевич Рымашевский, д.м.н., врач высшей квалификационной категории. Он является автором более 100 научных публикаций и методических рекомендаций. Александр Николаевич принимал участие в создании национального руководства по акушерству в 2007 г. По мнению член-корр. РАН, проф. В.Е. Радзинского, он является одним из корифеев отечественного акушерства [12]. Специалисты кафедры, руководимой д.м.н., проф. А.Н. Рымашевским, владеют самыми современными методиками диагностики и лечения. Основными направлениями кафедры являются проблемы перинатальной охраны плода, профилактика септических заболеваний в акушерско-гинекологической клинике. На кафедре освоены эндохирургические методы в оперативной гинекологии, в том числе операции высокой категории сложности (лапароскопически ассистированные влагалищные экстирпации), реконструктивные комбинированные операции при недержании мочи и опущении женских половых органов, освоены и внедрены в практику оригинальные методы хирургического лечения варикозной болезни таза, микрохирургические методы при лечении бесплодия.

Учитывая возросшую потребность в расширении учебной базы для целенаправленной и более качествен-

ной подготовки врачей и наличие подготовленных научных кадров, в 70-е гг. по инициативе П. Я. Лельчука были созданы ещё две кафедры акушерства и гинекологии — на педиатрическом факультете и на факультете усовершенствования врачей.

В начале от кафедры акушерства и гинекологии Ростовского медицинского института, которой заведовал проф. П.Я. Лельчук, был отделён самостоятельный курс для преподавания акушерства и гинекологии студентам педиатрического факультета. Возглавила курс к.м.н., доц. Валентина Петровна Юровская. Учебной базой курса стали родильный дом № 2 и гинекологическое отделение горбольницы № 6. В 1978 г. доцентский курс стал кафедрой акушерства и гинекологии № 2 педиатрического и санитарно-гигиенического факультетов. На протяжении многих лет начальником учебной части кафедры является к.м.н., доц. Е.П. Евдокимова. С момента создания курса, а затем и кафедры ею бессменно руководила проф. Валентина Петровна Юровская. Тема кандидатской и докторской диссертаций В.П. Юровской — «Материалы по изучению физиологии и патологии половой системы девочек раннего детского и дошкольного возраста» и «Синдром склерополикистозных яичников» — положили начало научным направлениями кафедры. С учётом профиля факультетов, на которых работает коллектив кафедры, и нужд практического здравоохранения научные исследования кафедры охватывали вопросы перинатальной охраны плода, гинекологии детского и подросткового возраста и влияния экологических факторов на женскую репродуктивную систему.

В 1985 г. проф. В.П. Юровской в соавторстве с ведущими учеными страны был написан учебник для студентов медицинских ВУЗов «Гинекология». В 2004 г. под её редакцией издан учебник «Гинекология детского и подросткового возраста», одним из авторов которого стала ученица Валентины Петровны, д.м.н. Чеботарева Юлия Юрьевна [13]. В.П. Юровская являлась автором более 250 научных статей, методических рекомендаций, учебников. Под её руководством защищено около 20 диссертаций, одна из них — докторская на тему «Механизмы формирования синдрома поликистозных яичников в периоде полового развития, клиническое течение, профилактика и лечение» [14, 15]. Последняя диссертация была посвящена возрастной эволюции синдрома поликистозных яичников, изучением которого В.П. Юровская занималась многие годы. Получено 3 авторских свидетельства, включая патент в области биологического моделирования СПКЯ (синдрома поликистозных яичников) [16]. За 40 лет на кафедре подготовлены сотни ординаторов и интернов, сегодня достойно трудящихся в ЛПУ города, области, страны. В области детской и подростковой гинекологии проводятся исследования, связанные с хронизацией воспалительных заболеваний вульвы и влагалища у молодых женщин [17].

Лечебная работа на кафедре выполняется на базах гинекологического отделения городской больницы № 6, с участием доцента кафедры Евдокимовой Е.П., к.м.н. Гречко Е.П., родильного отделения городской больницы № 6 — к.м.н. Подгорного И.В., детского акушерско-гинекологического кабинета МБУЗ «Детская поликлиника № 45» с участием доцента, д.м.н. Чеботаревой Ю.Ю.

В настоящее время кафедрой руководит д.м.н., проф. Петров Юрий Алексеевич. Его основной помощник — старший лаборант кафедры Рыжкина Ю.Н. Она ведёт всю документацию по кафедре и методическую работу.

В 1972 г. в связи с возрастающей потребностью в повышении квалификации специалистов по инициативе П.Я. Лельчука была сформирована самостоятельная кафедра акушерства и гинекологии № 3 ФПК и ППС, которую со дня основания и до 1986 г. возглавляла проф. Ольга Исааковна Барсукова. Проф. О.И. Барсукова — автор 150 научных работ. В их число входят исследования, посвящённые состоянию здоровья женщин, работающих в отраслях промышленности и на транспорте. Среди них — монография «Женская консультация» и углубленные разработки общих положений по темам «Женщина и производство», «Женщина и село» и др. С 1974 по 1986 гг. О.И. Барсукова являлась членом секции «Охрана женского труда» НИИ АМН СССР. Участвовала в создании всесоюзных программ по охране здоровья и труда женщин и международном конгрессе акушеров-гинекологов в 1973 г. в Москве. Награждена знаком «Отличник здравоохранения» [2, 4].

В 1986–1987 гг. обязанности заведующего кафедрой исполнял доц. Рудольф Александрович Лошенфельд. С 1987 по 2000 гг. кафедрой заведовал проф. Владимир Иванович Орлов, одновременно являясь директором Ростовского научно-исследовательского института акушерства и педиатрии, а с 2000 по 2010 гг. — д.м.н., проф. Ирина Олеговна Буштырева [1].

С 2010 г. руководит кафедрой заслуженный врач РФ, д.м.н., проф. Александр Феликсович Михельсон. Под его руководством научно-педагогический коллектив кафедры продолжает традиции выдающихся акушеров-гинекологов, профессоров, стоявших у истоков этой школы. Основными направлениями работы кафедры являются проблемы невынашивания и коррекции патологии развития беременности, миомы матки и беременности, нейроэндокринной патологии, дисбиотических нарушений микрофлоры влагалища, патологии шейки матки и молочных желез [1]. Научные исследования на кафедре проводятся в рамках комплексной целевой программы «Научно-организационные основы важнейших заболеваний матери и ребенка». Инновационным научным направлением кафедры является системный анализ критических акушерских состояний, едва не завершившихся летальным исходом — случаев «near of miss» (создана научно-исследовательская программа в рамках научно-практической школы «На грани акушерских потерь (near miss maternal morbidity)». Профессору кафедры Елизавете Юрьевне Лебеденко принадлежит первая в стране монография, посвященная данной проблеме [18]. Александр Феликсович — Председатель квалификационной (сертификационной) подкомиссии РостГМУ по специальности «Акушерство и гинекология», член Подкомиссии по акушерству и гинекологии Областной аттестационной комиссии, член Ученого совета РостГМУ МЗ РФ, член специализированных диссертационных советов РостГМУ и Волгоградского государственного медицинского университета, член научно-координационного совета по акушерству-гинекологии ФГБОУ ВО РостГМУ Минздрава России, член редакционного совета «Журнала прак-

тического врача акушера-гинеколога», издающегося в г. Волгограде. Александр Феликсович Михельсон награжден нагрудным знаком «Отличник здравоохранени», удостоен благодарственным письмом и грамотой Законодательного Собрания Ростовской области. За заслуги в области здравоохранения и многолетний добросовестный труд А.Ф. Михельсон награжден Почетной грамотой Министерства Здравоохранения Российской Федерации. Под его руководством научно-педагогический коллектив кафедры продолжает традиции выдающихся акушеров-гинекологов, профессоров, стоявших у истоков этой школы.

Выводы

На всех этапах развития Ростовская школа акушерства и гинекологии отличалась высоким профессионализмом, разработкой и внедрением перспективных новых направлений научной деятельности, работой по подготовке высокопрофессиональных специалистов в области акушерства и гинекологии.

Формирование школы акушерства и гинекологии характеризуется преемственностью в изучении патологических процессов, создании, освоении и внедрении новых методов и технологий консервативного и оперативного лечения. Большое место в этом принадлежит коллективной, слаженной работе поколений учеников и врачебным династиям.

Финансирование. Исследование не имело спонсорской поддержки.

Financing. *The study did not have sponsorship.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Conflict of interest. *Authors declares no conflict of interest.*

ЛИТЕРАТУРА

1. *Ростовский государственный университет: факультет, институт, университет.* Под ред. Сависько А. А. - Ростов -на-Дону.: ООО Омега Паблишер; 2010.
2. Панков Г.И., Зарубинская Л. Г. *Ростовский медицинский университет*. - Ростов-на-Дону.: Ростовский государственный медицинский университет; 1996. 128 с.
3. Сицинский А. А. *Лечение заразных послеродовых заболеваний в полости матки*. Санкт-Петербург; 1904.
4. Панков Г. И., Зарубинская Л. Г. *Хирургия на Дону: История и современность*. - Ростов н/Д.: РГУ Изд-во Ростовского университета; 1996.127с.
5. *Руководство по женским болезням*. Под ред. Кривского Л.А.- Л.: Практическая медицина; 1927.
6. Зарубинская Л.Г., Худоногов И.Ю. Профессор – гинеколог Петр Яковлевич Лельчук (К 120-летию со дня рождения). // *Международная научная конференция «Сточиковские чтения»; 25* мая 2018; Москва.
7. Лельчук П. Я. *Влияние инсулина на яичники и на некоторые другие железы внутренней секреции.* - Ростов н/Д.: Рост. мед. инст.;1937.
8. Лельчук П. Я. *Распознавание и лечение бесплодия женщин.* - Ростов н/Д.: Рост. мед. инст.; 1946.
9. *Репродуктивная функция в онтогенезе человека.* Под. ред. П. Я. Лельчук. - Ростов н/Д.: Изд-во Рост. ун-та; 1980.
10. Лельчук П. Я. *Диагностика сроков дородового отпуска.* - Ростов н/Д.: Рост. мед. инст.;1937.
11. Лельчук П. Я. *Женская консультация.* - Ростов н/Д.: Рост. мед. инст.; 1964.
12. Радзинский В.Е. *Акушерская агрессия, v.2.0.*- М.: Изд-во журнала Status Praesens; 2017.
13. Чеботарева Ю. Ю., Т. А. Яценко. *Гинекология детского и подросткового возраста.* - Ростов н/Д.; 2004. Сер. Высшее образование.
14. Чеботарева Ю.Ю. Механизмы формирования синдрома поликистозных яичников в периоде полового созревания, клиническое течение, профилактика, лечение.// *Міжнародний ендокринологічний журнал.*- 2011. – Т.6, №38.-С.105-114. eLIBRARY ID: 21181498
15. Чеботарева Ю.Ю., Овсянников В.Г. Моделирование поликистоза яичников. // *Патологическая физиология и экспериментальная терапия.*- 2009. - №3. – С.29-32. eLIBRARY ID: 13215379
16. Чеботарева Ю.Ю., Юровская В.П., Овсянников В.Г. Способ моделирования поликистозных яичников. Патент на изобретение RU 2337411; 2008.

REFERENCES

1. Savis'ko A. A., eds. *Rostov state University: faculty, Institute, University.* Rostov -na-Donu: OOO Omega Pablisher; 2010. (in Russ.).
2. Pankov G.I., Zarubinskaya L.G. *Rostov medical University.* Rostov-on-don.: Rostov state medical University; 1996. (in Russ.).
3. Sicinskij A. A. *Treatment of postpartum infectious diseases in the uterine cavity*. Sankt-Peterburg; 1904. (in Russ.).
4. Pankov G. I., Zarubinskaya L. G. *Surgery on the don: History and modernity.* Rostov n / D: RSU Publishing house of the Rostov University; 1996. (in Russ.)
5. Krivskij L.A., eds. *Guide to women's diseases.* L.: Practical medicine; 1927. (in Russ.).
6. Zarubinskaya L. G., Khudonogov I. Yu. *Professor-gynecologist Pyotr Yakovlevich Lelchuk (To the 120th anniversary of his birth)* In the collection: Stasikowski read the Materials of International scientific conference. 2018. P. 87-88. (in Russ.).
7. Lel'chuk P. Ja. *Influence of insulin on the ovaries and on some other endocrine glands.* Rostov n/D: Rost. med. ins.; 1937. (in Russ.).
8. Lel'chuk P. Ja. Recognition and treatment of infertility in women. Rostov n/D: Rost. med. ins.; 1946. (in Russ.).
9. Lel'chuk P. Ja., eds. *Reproductive function in human ontogenesis.* Rostov n/D: Rost. med. ins.; 1980. (in Russ.).
10. Lel'chuk P. Ja. *Women's consultation.* Rostov n/D: Rost. med. ins.; 1964. (in Russ.).
11. Lel'chuk P. Ja. *Diagnostics of prenatal leave terms.* Rostov n/D: Rost. med. ins.;1937. (in Russ.).
12. Radzinskij V.E. *Obstetric aggression, v.2.0.* M.: Status Praesens, 2017. (in Russ.).
13. Chebotareva Ju. Ju., Jacenko T. A. *Gynecology of children and adolescents.* Rostov n/D., 2004. (in Russ.).
14. Chebotareva Ju.Ju. Mechanisms of formation of polycystic ovary syndrome during puberty, clinical course, prevention, treatment. *Mizhnarodnij endokrinologichnij zhurnal.* 2011; 6 (38): 105-9. (in Russ.). eLIBRARY ID: 21181498
15. Chebotareva Yu.Yu., Ovsjannikov V.G. Modeling of polycystic ovaries *Pathological physiology and experimental therapy.* 2009; 3: 29-2. (in Russ.). eLIBRARY ID: 13215379
16. Chebotareva Yu.Yu., Jurovskaja V.P., Ovsjannikov V.G. Method for modeling polycystic ovaries. Patent RU N 2337411; 2008. (in Russ.).
17. Chebotaryova Yu.Yu., Kostoeva Z.A., Sultanova D.A. Clinical manifestations and treatment of chronical vulvovaginitis in

17. Chebotaryova Yu.Yu., Kostoeva Z.A., Sultanova D.A. Clinical manifestations and treatment of chronical vulvovaginitis in young women. // *Вопросы гинекологии, акушерства и перинатологии*. – 2018. - №2 (17). – С.22-5. https://doi.org/10.20953/1726-1678-2018-2-22-26
18. Лебеденко Е.Ю. *Near miss. На грани материнских потерь*. Под ред. В. Е. Радзинского. Москва: StatusPraesens; 2015.

Информация об авторах

Михельсон Александр Феликсович, д.м.н., профессор, заведующий кафедрой акушерства и гинекологии № 3, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0002-6792-0982. E-mail: michelson.a.f@mail.ru.

Чеботарева Юлия Юрьевна, д.м.н., доцент кафедры акушерства и гинекологии №2, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0001-9609-0917. E-mail: chebotarevajulia@inbox.ru.

Евдокимова Елена Петровна, к.м.н., доцент кафедры акушерства и гинекологии №2, Ростовский государственный медицинский университет, Ростов-на-Дону, Россия. ORCID: 0000-0001-6812-6038. E-mail: evdokimovadoc@mail.ru.

Вклад авторов

А.Ф. Михельсон — разработка дизайна исследования;
Е.П. Евдокимова — получение и анализ данных;
А.Ф. Михельсон, Ю.Ю. Чеботарева — написание текста рукописи.

Получено / Recived: 04.12.2020
Принято к печати / Accepted: 07.12.2020

young women. *Voprosy ginekologii, akusherstva i perinatologii*. 2018;2(17):22-5. (in Russ.). https://doi.org/10.20953/1726-1678-2018-2-22-26
18. Lebedenko E.Ju. Near miss. On the verge of maternal losses; ed. by V. E. Radzinsky. Moskva: StatusPraesens, 2015. (in Russ.).

Information about the authors

Alexandr F. Mikhelson, Dr. Sci. (Med.), Professor, head of the Department of obstetrics and gynecology No. 3, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0002-6792-0982. E-mail: michelson.a.f@mail.ru.

Yulia Yu. Chebotareva, Dr. Sci. (Med.), associate Professor of the Department of obstetrics and gynecology No. 2, Rostov state medical University, Rostov-on-Don, Russia. ORCID: 0000-0001-9609-0917. E-mail: chebotarevajulia@inbox.ru.

Elena P. Evdokimova, Cand. Sci. (Med.), associate Professor of obstetrics and gynecology Department no. 2, Rostov State Medical University, Rostov-on-Don, Russia. ORCID: 0000-0001-6812-6038. E-mail: evdokimovadoc@mail.ru.

Authors contribution

A. F. Mikhelson — research design development;
Yu. Yu. Chebotareva, E. P. Evdokimova— obtaining and analysis of the data;
A. F. Mikhelson, Yu. Yu. Chebotareva — writing the text of the manuscript.