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SARS COV-2 DELTA VARIANT STRUCTURAL PROTEINS: HOMOLOGY WITH OPPORTUNISTIC BACTERIA

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Abstract. The capacity of SARS CoV-2 for immune evasion can be considered universally recognized. Coronavirus and human protein homology may be one of the mechanisms of immune evasion. Delta variant necessarily has structural features that explain its specific qualities. The aim of our study is to find out whether mutations in the structural proteins of Delta variant change its homology with proteins present in the human body, i.e. human, bacterial and dietary. Using bioinformatics tools we detected homology on the heptamer level between Delta variant structural proteins and human proteins as well as some opportunistic bacteria proteins of the upper respiratory tract, lung and gut. Delta variant spike (S) and membrane (M) proteins have a large number of similarities (homologous correspondences) with the listed proteins, with the S:Δ156,157;R158G mutation having the greatest amount. The reason why SARS CoV-2 Delta variant has specific characteristics, most importantly increased lethality, is most likely to be found in a mutation at positions 156–158 of spike protein.

Keywords: SARS CoV-2, Delta variant, spike protein, opportunistic bacteria, homology

СТРУКТУРНЫЕ БЕЛКИ ДЕЛЬТА-ВАРИАНТА SARS COV-2: ГОМОЛОГИЯ С ОППОРТУНИСТИЧЕСКИМИ БАКТЕРИЯМИ

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Резюме. Способность SARS CoV-2 уклоняться от иммунного ответа можно считать общепризнанной. Гомология белков коронавируса и человека может быть одним из механизмов иммунного уклонения. Дельта-вариант обязательно имеет структурные особенности, которые объясняют его специфические свойства. Целью нашего исследования было выяснить, изменяют ли мутации, произошедшие в структурных белках дельта-варианта, его гомологию с белками, присутствующими в организме человека, то есть собственно человеческими, бактериальными и пищевыми. Используя инструменты биоинформатики, мы обнаружили гомологию на уровне гептамеров между структурными белками дельта-варианта и белками человека, а также белками некоторых

условно-патогенных бактерий верхних дыхательных путей, легких и кишечника. Белки шиповый (S) и мембранный (M) дельта-варианта имеют большое количество сходств (гомологичных соответствий) с перечисленными белками, причем наибольшее количество — в случае мутации S:Δ156,157;R158G. Причина, по которой дельта-вариант SARS CoV-2 обладает специфическими характеристиками, и прежде всего повышенной летальностью, скорее всего, кроется в мутации в положениях 156–158 шипового белка.

Ключевые слова: SARS CoV-2, дельта-вариант, шиповидный белок, оппортунистические бактерии, гомология

INTRODUCTION

After a series of brilliant discoveries from Pasteur to Fleming and Waxman, mankind has learned to control most *bacterial infections.* Humans were able to create megalopolises with huge population densities. In response, nature had to put forward other limiting mechanisms less humanly controllable. The COVID-19 pandemic has become and will remain one of humanity's major concerns for the near future. The very important question is why and how this CoV could cause a pandemic [1]. Some mutation-induced structural substitutions in the N-terminal domain (NTD) of the SARS-CoV-2 S-protein lead to more efficient first contact and interaction with the upper airway epithelium [2].

The extraordinary virulence of Omicron variant (B.1.1.529) is now the main focus of researchers [3]. Nevertheless, it seems to us that in order to understand the causes of SARS CoV-2 *lethality*, the peculiarities of *Delta* variant (B.1.617.2) must be studied.

Using 3D models, the researchers can determine how the spike (S) protein binds to the ACE2 receptor [4]. The peculiarity of our approach is that we seek an explanation for the properties of coronavirus in the homology (commonality of short motifs) of virus proteins with human proteins. Recently we described dozens of homologous motifs in the primary structure of SARS CoV-2 and human proteins including proteins of olfactory and taste receptors [5]. Through mutations, the virus finds a way to avoid an immune response [6].

Molecular mimicry is considered a strategy used by many viruses to subvert and regulate antiviral immunity. For example, human cytomegalovirus has hijacked or developed a number of homologous sites that mimic immunomodulatory proteins encoded by the human body. These homologues encoded by the virus can contribute to the virus' evasion of immune clearance [7].

Following Joshua Lederberg's principle [8], we took into account not only proteins synthesized by the human body, but also those that originate from other genotypes and are constantly present in the macroorganism. These are the proteins of *commensal and opportunistic bacteria* of the upper respiratory tract, lung, oral cavity, and GI tract. We also analyzed the most common dietary proteins that are almost constantly present in the gut, namely those of the six world's most important cereal crops, i.e., Asian *rice Oryza sativa*, common wheat *Triticum aestivum*, maize *Zea mays*, common bean *Phaseolus vulgaris,* barley *Hordeum vulgare*, and sorghum *Sorghum bicolor*. We believed that the homology of the virus proteins with those of the named bacteria and cereals helps coronavirus to avoid or reduce the primary immune response.

THE AIM OF OUR STUDY

The aim of our study is to find out whether mutations in the structural proteins of SARS CoV-2 Delta variant change its homology with proteins present in the human body, i.e. human, bacterial and dietary.

RESULTS

Spike glycoprotein

Wuhan-Hu spike glycoprotein (S protein) molecule consists of 1273 amino acid residues. In Delta variant, as a result of two deletions ($E_{156}\Delta$ and $F_{157}\Delta$), S protein consists of 1271 amino acid residues and contains seven substitutions in nine positions, namely $T_{19}R$, $G_{142}D$, $R_{158}G$, $L_{452}R$, $T_{478}K$, $P_{681}H$, and $D_{950}N$, numeration as in Wuhan-Hu variant [9].

S protein Delta variant, 1271 aa

MFVFLVLLPLVSSQCVNLR**TRTQLPPAYTNSFTRGVYYP**
DKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGT
KRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQ
SLLIVNNATNVVIKVCEFQFCNDPFLD**VYYHKNNKSWMES**
GVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREF
VFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINI
TRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRT
FLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSN
F*RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRIS*
NCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSF
*VIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWN*SNNLD
SKVGGNYNY**R**YRLFRKSNLKPFERDISTEIYQAGS**K**PCNG
*VEGFNCYFPLQSYGFQPTNGVGYQPY**RVVVLSFELLHAPAT***
*VCGPKKSTNLVKNKCVNF***NFNGLTGTGVLTESNKKFLPFQQF**
GRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQ
VAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGC
LIGAEHVNNSYECDIPIGAGICASYQTQTNSRRRARSVAS

QSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTK
TSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQD
KNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRS
FIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFN
GLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAA
LQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIG
KIQDSLSSTASALGKLQNVVNQNAQALNTLVKQLSS
NFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSL
QTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDF
CGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAI
CHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNT
FVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKN
HTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNES
LIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCC
MTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

Hereinafter, motifs homologous with human proteins [5] are highlighted in red font. Amino acid residues substituted as a result of mutations are highlighted in large letters. The N-terminal domain (NTD_{14-303}) is highlighted in green. Receptor-binding domain ($RBD_{317-539}$) is in gray italics. Receptor-binding motif $RBM_{436-506}$ is underlined. Heptapeptide repeat sequence 1 ($HR1_{910-982}$) is highlighted in blue. As a result of the double deletion $\Delta_{156,157}$, starting from G_{156}, the numbering of positions in Delta variant does not correspond to the numbering in Wuhan-Hu.

Delta variant, as mentioned above, has a mutation $S:P_{681}H$. The S protein motif $SPRRARS_{680-686}$ homologous with a human protein has been replaced by a heptamer $SHRRARS_{678-684}$, which has no homologues in mammals (Table 1).

Table 1

Homology of a SARS CoV-2 S protein to a human protein

Mutation	Wuhan-Hu			Delta		
$P_{681}H^*$	S protein heptamer	Species	Homologous protein heptamer	S protein heptamer	Species	Homologous protein heptamer
	$SPRRARS_{680-686}{}^*$	*Homo sapiens*	Hermansky-Pudlak syndrome 1 $protein_{258-264}$	$SHRRARS_{678-684}$	No homological heptamers in commensal	

*In Wuhan-Hu and Delta variants, the position numbering differs after position 156 as a result of the Δ156,157 deletions.

The heptamers of S protein that are homologous with the proteins of some commensal and opportunistic bacteria are listed in Table 2.

Table 2

The heptamers of S protein homologous with the proteins of some commensal and opportunistic bacteria

Mutation	Wuhan-Hu				Delta			
	S protein heptamer	Species	Homologous protein heptamer	Localization in the human body	S protein heptamer	Species	Homologous protein heptamer	Localization in the human body
$T_{19}R$	$VNLTTRT_{16-22}$	*Escherichia coli BCE011_MS-01*	Uncharacterized $protein_{23-29}$	gut	$VNLRTRT_{16-22}$	*Streptococcus mitis SK597 TnpX; Streptococcus salivarius (strain CCHSS3)*	Site-specific recombinase$_{275-281}$	nasopharynx, oral cavity, throat
	$NLTTRTQ_{17-23}$	*Enterococcus faecalis*	Helicase, RecD/TraA $family_{755-761}$	gut	$NLRTRTQ_{17-23}$	*Subdoligranulum variabile*	Putative hydrolase$_{34-40}$	gut
$G_{142}D^*$	$NDPFLGV_{137-143}$	No homological heptamers in commensal or opportunistic bacteria			$NDPFLDV_{137-143}$	*Pasteurella multocida subsp. multocida str*	Release factor glutamine methyltransferase$_{20-26}$	lung
Δ156, 157; R158G	$EFRVYSS_{156-162}$	No homological heptamers in commensal or opportunistic bacteria			$ESGVYSS_{154-160}$	*Lachnospiraceae bacterium 7_1_58FAA*	Uncharacterized protein$_{126-132}$	gut
						Escherichia coli UMEA 3609-1	Valine–tRNA ligase$_{320-326}$	gut

Endind of the table 2

Mutation	Wuhan-Hu				Delta			
	S protein heptamer	Species	Homologous protein heptamer	Localization in the human body	S protein heptamer	Species	Homologous protein heptamer	Localization in the human body
	FRVYSSA$_{157-163}$	No homological heptamers in commensal or opportunistic bacteria			SGVYSSA$_{155-161}$	*Fusobacterium sp. oral taxon 370 str. F0437*	Hep/Hag repeat protein (Fragment)$_{47-53}$	oral cavity
	RVYSSAN$_{158-164}$	*Bifidobacterium animalis subsp. lactis CNCM I-2494*	Fibronectin-binding protein$_{191-197}$	gut	GVYSSAN$_{156-162}$	*Bacillus sp. NRRL B-14911*	Methylmalonyl-CoA mutase$_{565-571}$	?
						Lactobacillus farraginis JCM 14108	D-alanyl-D-alanine carboxypeptidase$_{149-155}$	gut
						Fusobacterium nucleatum subsp. polymorphum F0401	Uncharacterized protein$_{234-240}$	oral cavity
						Prevotella saccharolytica F0055	Carbohydrate binding domain protein$_{715-721}$	oral cavity, upper respiratory tract, gut
						human gut metagenome	Glycoside hydrolase, family 25 (Fragment)$_{395-401}$	gut
$L_{452}R$	No homological heptamers in commensal or opportunistic bacteria							
$T_{478}K^*$	No homological heptamers in commensal or opportunistic bacteria							
$P_{681}H^*$	NSPRRAR$_{679-685}$	No homological heptamers in commensal or opportunistic bacteria			NSHRRAR$_{677-683}$	*Clostridium clostridioforme*	Uncharacterized protein$_{116-122}$	gut
$D_{950}N^*$	KLQDVVN$_{947-953}$	*Prevotella salivae F0493*	Peptidase M16 inactive domain protein$_{918-924}$	oral cavity, gut	KLQNVVN$_{945-951}$	*Leptotrichia buccalis (strain ATCC 14201 / DSM 1135 / JCM 12969 / NCTC 10249)*	GCN5-related N-acetyltransferase$_{115-121}$	oral cavity
	DVVNQNA$_{950-956}$	No homological heptamers in commensal or opportunistic bacteria			NVVNQNA$_{948-954}$	*Prevotella multisaccharivorax DSM 17128*	Anaerobic ribonucleoside-triphosphate reductase$_{114-120}$	oral cavity, gut

*The same mutation has occurred in Omicron variant.

The heptamers of S protein that are homologous with the most common cereal proteins are listed in Table 3.

Table 3

The heptamers of S protein homologous with the most common cereal proteins

Mutation	Wuhan-Hu			Delta		
	S protein heptamer	Species	Homologous protein heptamer	S protein heptamer	Species	Homologous protein heptamer
$T_{19}R$	SQCVNLT$_{13-19}$	*Oryza sativa*	Leucine Rich Repeat family protein, expressed$_{520-526}$	SQCVNLR$_{13-19}$	No most common cereal sample	
	VNLTTRT$_{16-22}$	*Oryza sativa BCE011_MS-01*	Uncharacterized protein$_{23-29}$	VNLRTRT$_{16-22}$	No most common cereal sample	
	LTTRTQL$_{18-24}$	*Triticum aestivum*	Uncharacterized protein$_{888-894}$	LRTRTQL$_{18-24}$	No most common cereal sample	

Endind of the table 3

Mutation	Wuhan-Hu			Delta		
	S protein heptamer	Species	Homologous protein heptamer	S protein heptamer	Species	Homologous protein heptamer
$L_{452}R$	$LYRLFRK_{452-458}$	*Oryza sativa subsp. indica*	Putative uncharacterized protein$_{157-163}$	$RYRLFRK_{450-456}$	No most common cereal sample	
		Zea mays	Putative NAC domain transcription factor superfamily protein (Fragment)$_{100-106}$			
$T_{478}K^*$	$sTPCNGV_{477-483}$	No most common cereal sample		$sKPCNGV_{475-481}$	*Phaseolus vulgaris*	Uncharacterized protein$_{59-65}$
	$sPRRARS_{680-686}$	*Oryza sativa subsp. japonica*	Os02g0817400 protein (Fragment)$_{1-7}$	$sHRRARS_{678-684}$	*Oryza sativa subsp. japonica*	Expressed protein$_{296-302}$
		Zea mays	Uncharacterized protein$_{58-64}$		*Oryza sativa subsp. japonica*	Uncharacterized protein$_{616-622}$
					Hordeum vulgare	Predicted protein (Fragment)$_{16-22}$
	$PRRARSV_{681-687}$	*Oryza sativa subsp. japonica*	Putative uncharacterized protein$_{118-124}$	$HRRARSV_{679-685}$	No most common cereal sample	
		Zea mays	Uncharacterized protein$_{94-100}$			
$\mathbf{D_{950}N^*}$	$\mathbf{ALGKLQD_{844-950}}$	*Hordeum vulgare var. distichum*	Uncharacterized protein$_{123-129}$	$ALGKLQN_{842-848}$	No most commoncereal sample	
	$\mathbf{LGKLQDV_{945-951}}$	*Hordeum vulgare var. distichum*	Uncharacterized protein$_{96-102}$	$LGKLQNV_{843-849}$	No most common cereal sample	
		Oryza sativa subsp. indica	Uncharacterized protein$_{248-254}$			
		Zea mays	Protein Iap4$_{233-239}$			
			Golgi SNAP receptor complex member 1$_{75-81}$			
	$GKLQDVV_{946-952}$	*Zea mays*	Uncharacterized protein$_{388-394}$	$GKLQNVV_{844-850}$	No most common cereal sample	

*The same mutation has occurred in Omicron variant.

The heptamers of S protein that are homologous with some virus proteins are listed in Table 4.

Table 4

The heptamers of S protein homologous with some virus proteins

Mutation	Wuhan-Hu			Delta			Comment
	S protein heptamer	Other virus	Homologous protein heptamer	S protein heptamer	Other viruses	Homologous protein heptamer	
$P_{681}H$	$QTQTNSP_{675-681}$	*Human immunodeficiency virus 1*	Protease (Fragment)$_{2-7}$	$QTQTNSH_{673-679}$	No virus proteins homology		Homology with HIV-1 has disappeared
$\mathbf{D_{950}N^*}$	$LQDVVNQ_{948-954}$	No virus proteins homology		$LQNVVNQ_{946-952}$	*Human immunodeficiency virus 1*	Envelope glycoprotein (Fragment)$_{71-77}$	Homology with HIV-1 has appeared

* The same mutation has occurred in Omicron variant.

Membrane protein

There are four mutations known in the membrane (M) protein Delta variant, namely A_2S, $F_{28}L$, $V_{70}L$, and $I_{82}T$ [10].

M protein Delta variant, 222 aa

MSDSNGTITVEELKKLLEQWNLVIGFLLLTWICLLQFAYANR
NRFLYIIKLIFLWLLWPVTLACFVLAALYRINWITGGIATAMACLV

GLMWLSYFIASFRLFARTRSMWSFNPETNILLNVPLHGTILTRP
LLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSYY
KLGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSDNIALLVQ

The heptamers of M protein that are homologous with the proteins of the commensal and opportunistic bacteria are listed in Table 5.

Table 5

The heptamers of M protein homologous with the proteins of the commensal and opportunistic bacteria

Mutation	Wuhan-Hu				Delta			
	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body
A_2S	M**A**DSNGT$_{1-7}$	No homological heptamers in commensal or opportunistic bacteria			M**S**DSNGT$_{1-7}$	No homological heptamers in commensal or opportunistic bacteria		
	ADSNGTI$_{2-8}$	*Lachnospiraceae bacterium 7_1_58FAA*	Uncharacterized protein$_{252-258}$	gut	**S**DSNGTI$_{2-8}$			
$F_{28}L$	LVIGFL**F**$_{22-28}$	*Enterococcus faecalis R508*	Putative ferrichrome transport system permease protein FhuG$_{203-206}$	gut	LVIGFLL$_{22-28}$	*Eubacterium ventriosum ATCC 27560*	Putative K(+)-stimulated pyrophosphate-energized sodium pump$_{573-579}$	gut
						Enterococcus caccae ATCC BAA-1240	Uncharacterized protein$_{104-110}$	gut
						Faecalibacterium sp. CAG:74	Binding-protein-dependent transport systems inner membrane component$_{86-92}$	gut
						Prevotella histicola F0411	Uncharacterized protein$_{15-21}$	gut
						Lachnospiraceae bacterium 2_1_58FAA	Uncharacterized protein$_{65-71}$	gut
						Escherichia coli ISC11	Putative cell envelope opacity-associated protein A$_{42-48}$	gut
	VIGFL**F**L$_{23-29}$	*Enterococcus flavescens ATCC 49996*	Uncharacterized protein$_{128-134}$	gut	VIGFL**L**L$_{23-29}$	*Prevotella sp. oral taxon 472 str. F0295*	Uncharacterized protein$_{178-184}$	gut
		Lachnospiraceae bacterium COE1	MATE efflux family protein112-118	gut		*Lactobacillus brevis ATCC 14869 = DSM 20054*	Potassium uptake protein, TrkH family$_{239-245}$	gut
						Lactobacillus antri DSM 16041	Transporter, major facilitator family protein$_{422-428}$	gut
						Enterobacter cloacae subsp. cloacae (strain ATCC 13047 / DSM 30054 / NBRC 13535 / NCDC 279-56)	Putative multidrug resistance protein MdtD$_{183-189}$	gut
						Lachnospiraceae bacterium 28-4	Uncharacterized protein$_{18-24}$	gut
	IGFL**F**LT$_{24-30}$	*Lachnospiraceae bacterium CAG:215*	Transporter$_{468-474}$	gut	IGFL**L**LT$_{24-30}$	*Lactobacillus paracasei subsp. paracasei Lpp126*	Oligopeptide transport system permease protein oppB$_{9-15}$	oral cavity
						Eubacterium nodatum ATCC 33099	TIGR02185 family protein$_{43-49}$	oral cavity
						Bacteroides uniformis dnLKV2	Uncharacterized protein$_{737-743}$	gut
						Escherichia coli 2845650	Uncharacterized protein$_{13-19}$	gut
						Prevotella sp. CAG:1320	Putative thiol:disulfide interchange protein DsbD$_{8-14}$	gut
						Enterococcus faecalis 06-MB-DW-09	Putative transmembrane permease MsmF$_{16-22}$	gut
	GFL**F**LTW$_{25-31}$	No homological heptamers in commensal or opportunistic bacteria			GFL**L**LTW$_{25-31}$	No homological heptamers in commensal or opportunistic bacteria		

Endind of the table 5

Mutation	Wuhan-Hu				Delta			
	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body
	FL**F**LTWI$_{26-32}$	No homological heptamers in commensal or opportunistic bacteria			FL**L**LTWI$_{26-32}$	No homological heptamers in commensal or opportunistic bacteria		
	L**F**LTWIC$_{27-33}$	No homological heptamers in commensal or opportunistic bacteria			L**L**LTWIC$_{27-33}$	*Peptoniphilus sp. oral taxon 375 str. F0436*	Na+/H+ antiporter family protein$_{105-111}$	gut
	FLTWICL$_{28-34}$	No homological heptamers in commensal or opportunistic bacteria			**L**LTWICL$_{28-34}$	No homological heptamers in commensal or opportunistic bacteria		
$V_{70}L$	CFVLAA**V**$_{64-70}$	*Enterobacter sp. Ag1*	Formate dehydrogenase-O subunit gamma$_{24-30}$	gut	CFVLAA**L**$_{64-70}$	No homological heptamers in commensal or opportunistic bacteria		
	FVLAA**V**Y$_{65-71}$	No homological heptamers in commensal or opportunistic bacteria			FVLAA**L**Y$_{65-71}$	*Bacteroides dorei CL03T12C01*	HAD hydrolase, family IA$_{344-350}$	gut
	VLAA**V**YR$_{66-72}$	No homological heptamers in commensal or opportunistic bacteria			VLAA**L**YR$_{66-72}$	*Bifidobacterium longum subsp. infantis (strain ATCC 15697 / DSM 20088 / JCM 1222 / NCTC 11817 / S12)*	Putative ABC transporter permease component$_{110-116}$	gut
						Haemophilus parainfluenzae ATCC 33392	ABC transporter, permease protein$_{121-127}$	upper respiratory tract, lung
	LAA**V**YRI$_{67-73}$	*Lachnospiraceae bacterium 3_1_57FAA_CT1*	Uncharacterized protein$_{130-136}$	gut	LAA**L**YRI$_{67-73}$	*Acinetobacter sp. CIP 101966*	Uncharacterized protein$_{18-24}$	oral cavity
	AA**V**YRIN$_{68-74}$	*Lautropia mirabilis ATCC 51599*	Selenide, water dikinase$_{56-62}$	oral cavity, upper respiratory tract	AA**L**YRIN$_{68-74}$	*Prevotella melaninogenica (strain ATCC 25845 / DSM 7089 / JCM 6325 / VPI 2381 / B282) GN=HMPREF0659_A647*	Hydrolase, NUDIX family$_{54-60}$	upper respiratory tract
		Lachnospiraceae bacterium JC7	Diguanylate cyclase (GGDEF) domain-containing protein (Precursor)$_{114-120}$	gut		*Lactobacillus ruminis (strain ATCC 27782 / RF3)*	Conserved hypothetical YitT family protein	gut
						Bacteroides nordii CL02T12C05	Uncharacterized protein$_{700-706}$	gut
	A**V**YRINW$_{69-75}$	No homological heptamers in commensal or opportunistic bacteria			A**L**YRINW$_{69-75}$	No homological heptamers in commensal or opportunistic bacteria		
	VYRINWI$_{70-76}$	No homological heptamers in commensal or opportunistic bacteria			**L**YRINWI$_{70-76}$	No homological heptamers in commensal or opportunistic bacteria		
$I_{82}T$	ITGGIA**I**$_{76-82}$	*Ruminococcus obeum ATCC 29174*	Ion channel$_{143-149}$	gut	ITGGIA**T**$_{76-82}$	*Enterococcus faecalis*	Dephospho-CoA kinase$_{7-13}$	gut
		Bacteroides sp. 3_1_19	Putative uncharacterized protein$_{158-164}$	gut		*Clostridium asparagiforme DSM 15981*	ABC transporter, permease protein$_{268-274}$	gut
	TGGIA**I**A$_{77-83}$	No homological heptamers in commensal or opportunistic bacteria			TGGIA**T**A$_{77-83}$	*Veillonella sp. oral taxon 780 str. F0422*	PrpF protein$_{312-318}$	oral cavity
	GGIA**I**AM$_{78-84}$	*Enterobacteriaceae bacterium 9_2_54FAA*	Uncharacterized protein$_{270-276}$	gut	GGIA**T**AM$_{78-84}$	No homological heptamers in commensal or opportunistic bacteria		
		Eubacterium sulci ATCC 35585	Peptidase, M20/M25/M40 family$_{136-142}$	gut				
		Lactobacillus brevis subsp. gravesensis ATCC 27305	Transporter, major facilitator family protein$_{421-427}$	gut				
	GIA**I**AMA$_{79-85}$	*Lachnospiraceae bacterium 10-1*	Uncharacterized protein$_{148-154}$	gut	GIA**T**AMA$_{79-85}$	*Enterobacter aerogenes UCI 48*	Uncharacterized protein$_{320-326}$	gut
	IA**I**AMAC$_{80-86}$	No homological heptamers in commensal or opportunistic bacteria			IA**T**AMAC$_{80-86}$	No homological heptamers in commensal or opportunistic bacteria		
	A**I**AMACL$_{81-87}$	No homological heptamers in commensal or opportunistic bacteria			A**T**AMACL$_{81-87}$	*Lactobacillus paracasei subsp. paracasei CNCM I-4649*	Class II aldolase/adducin family protein$_{101-107}$	oral cavity, gut
	IAMACLV$_{82-88}$	No homological heptamers in commensal or opportunistic bacteria			**T**AMACLV$_{82-88}$	No homological heptamers in commensal or opportunistic bacteria		

*The same mutation has occurred in Omicron variant.

Membrane protein

There are four mutations known in the membrane (M) protein Delta variant, namely A_2S, $F_{28}L$, $V_{70}L$, and $I_{82}T$ [10].

M protein Delta variant, 222 aa

MSDSNGTITVEELKKLLEQWNLVIGFLLLTWICLLQFAYANRN RFLYIIKLIFLWLLWPVTLACFVLAALYRINWITGGIATAMACL VGLMWLSYFIASFRLFARTRSMWSFNPETNILLNVPLHGTILT RPLLESELVIGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSR TLSYYKLGASQRVAGDSGFAAYSRYRIGNYKLNTDHSSSSD NIALLVQ

The heptamers of M protein that are homologous with the proteins of the commensal and opportunistic bacteria are listed in Table 6.

Table 6

The heptamers of M protein homologous with the proteins of the commensal and opportunistic bacteria

Mutation	Wuhan-Hu				Delta			
	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body
A_2S	M**A**DSNGT$_{1-7}$	No homological heptamers in commensal or opportunistic bacteria			M**S**DSNGT$_{1-7}$	No homological heptamers in commensal or opportunistic bacteria		
	ADSNGTI$_{2-8}$	*Lachnospiraceae bacterium 7_1_58FAA*	Uncharacterized protein$_{252-258}$	gut	**S**DSNGTI$_{2-8}$			
$F_{28}L$	LVIGFL**F**$_{22-28}$	*Enterococcus faecalis R508*	Putative ferrichrome transport system permease protein FhuG$_{203-206}$	gut	LVIGFL**L**$_{22-28}$	*Eubacterium ventriosum ATCC 27560*	Putative K(+)-stimulated pyrophosphate-energized sodium pump$_{573-579}$	gut
						Enterococcus caccae ATCC BAA-1240	Uncharacterized protein $_{104-110}$	gut
						Faecalibacterium sp. CAG:74	Binding-protein-dependent transport systems inner membrane component$_{86-92}$	gut
						Prevotella histicola F0411	Uncharacterized protein $_{15-21}$	gut
						Lachnospiraceae bacterium 2_1_58FAA	Uncharacterized protein$_{65-71}$	gut
						Escherichia coli ISC11	Putative cell envelope opacity-associated protein A$_{42-48}$	gut
	VIGFL**F**L$_{23-29}$	*Enterococcus flavescens ATCC 49996*	Uncharacterized protein$_{128-134}$	gut	VIGFL**L**L$_{23-29}$	*Prevotella sp. oral taxon 472 str. F0295*	Uncharacterized protein$_{178-184}$	gut
		Lachnospiraceae bacterium COE1	MATE efflux family protein112-118	gut		*Lactobacillus brevis ATCC 14869 = DSM 20054*	Potassium uptake protein, TrkH family$_{239-245}$	gut
						Lactobacillus antri DSM 16041	Transporter, major facilitator family protein$_{422-428}$	gut
						Enterobacter cloacae subsp. cloacae (strain ATCC 13047 / DSM 30054 / NBRC 13535 / NCDC 279-56)	Putative multidrug resistance protein MdtD$_{183-189}$	gut
						Lachnospiraceae bacterium 28-4	Uncharacterized protein$_{18-24}$	gut
	IGFL**F**LT$_{24-30}$	*Lachnospiraceae bacterium CAG:215*	Transporter$_{468-474}$	gut[9	IGFL**L**LT$_{24-30}$	*Lactobacillus paracasei subsp. paracasei Lpp126*	Oligopeptide transport system permease protein oppB$_{9-15}$	oral cavity
						Eubacterium nodatum ATCC 33099	TIGR02185 family protein$_{43-49}$	oral cavity
						Bacteroides uniformis dnLKV2	Uncharacterized protein$_{737-743}$	gut
						Escherichia coli 2845650	Uncharacterized protein$_{13-19}$	gut
						Prevotella sp. CAG:1320	Putative thiol:disulfide interchange protein DsbD$_{8-14}$	gut
						Enterococcus faecalis 06-MB-DW-09	Putative transmembrane permease MsmF$_{16-22}$	gut
	GFL**F**LTW$_{25-31}$	No homological heptamers in commensal or opportunistic bacteria			GFL**L**LTW$_{25-31}$	No homological heptamers in commensal or opportunistic bacteria		

Endind of the table 6

Mutation	Wuhan-Hu				Delta			
	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body	M protein heptamer	Species	Homologous protein heptamer	Localization in the human body
	FL**F**LTWI$_{26-32}$	No homological heptamers in commensal or opportunistic bacteria			FL**L**LTWI$_{26-32}$	No homological heptamers in commensal or opportunistic bacteria		
	L**F**LTWIC$_{27-33}$	No homological heptamers in commensal or opportunistic bacteria			L**L**LTWIC$_{27-33}$	*Peptoniphilus sp. oral taxon 375 str. F0436*	Na+/H+ antiporter family protein$_{105-111}$	gut
	FLTWICL$_{28-34}$	No homological heptamers in commensal or opportunistic bacteria			**L**LTWICL$_{28-34}$	No homological heptamers in commensal or opportunistic bacteria		
$V_{70}L$	CFVLAA**V**$_{64-70}$	*Enterobacter sp. Ag1*	Formate dehydrogenase-O subunit gamma$_{24-30}$	gut	CFVLAA**L**$_{64-70}$	No homological heptamers in commensal or opportunistic bacteria		
	FVLAA**V**Y$_{65-71}$	No homological heptamers in commensal or opportunistic bacteria			FVLAA**L**Y$_{65-71}$	*Bacteroides dorei CL03T12C01*	HAD hydrolase, family IA$_{344-350}$	gut
	VLAA**V**YR$_{66-72}$	No homological heptamers in commensal or opportunistic bacteria			VLAA**L**YR$_{66-72}$	*Bifidobacterium longum subsp. infantis (strain ATCC 15697 / DSM 20088 / JCM 1222 / NCTC 11817 / S12)*	Putative ABC transporter permease component$_{110-116}$	gut
						Haemophilus parainfluenzae ATCC 33392	ABC transporter, permease protein$_{121-127}$	upper respiratory tract, lung
	LAA**V**YRI$_{67-73}$	*Lachnospiraceae bacterium 3_1_57FAA_CT1*	Uncharacterized protein$_{130-136}$	gut	LAA**L**YRI$_{67-73}$	*Acinetobacter sp. CIP 101966*	Uncharacterized protein$_{18-24}$	oral cavity
	AA**V**YRIN$_{68-74}$	*Lautropia mirabilis ATCC 51599*	Selenide, water dikinase$_{56-62}$	oral cavity, upper respiratory tract	AA**L**YRIN$_{68-74}$	*Prevotella melaninogenica (strain ATCC 25845 / DSM 7089 / JCM 6325 / VPI 2381 / B282) GN=HMPREF0659_A647*	Hydrolase, NUDIX family$_{54-60}$	upper respiratory tract
		Lachnospiraceae bacterium JC7	Diguanylate cyclase (GGDEF) domain-containing protein (Precursor)$_{114-120}$	gut		*Lactobacillus ruminis (strain ATCC 27782 / RF3)*	Conserved hypothetical YitT family protein	gut
						Bacteroides nordii CL02T12C05	Uncharacterized protein$_{700-706}$	gut
	A**V**YRINW$_{69-75}$	No homological heptamers in commensal or opportunistic bacteria			A**L**YRINW$_{69-75}$	No homological heptamers in commensal or opportunistic bacteria		
	VYRINWI$_{70-76}$	No homological heptamers in commensal or opportunistic bacteria			**L**YRINWI$_{70-76}$	No homological heptamers in commensal or opportunistic bacteria		
$I_{82}T$	ITGGIA**I**$_{76-82}$	*Ruminococcus obeum ATCC 29174*	Ion channel$_{143-149}$	gut	ITGGIA**T**$_{76-82}$	*Enterococcus faecalis*	Dephospho-CoA kinase$_{7-13}$	gut
		Bacteroides sp. 3_1_19	Putative uncharacterized protein$_{158-164}$	gut		*Clostridium asparagiforme DSM 15981*	ABC transporter, permease protein$_{268-274}$	gut
	TGGIA**I**A$_{77-83}$	No homological heptamers in commensal or opportunistic bacteria			TGGIA**T**A$_{77-83}$	*Veillonella sp. oral taxon 780 str. F0422*	PrpF protein$_{312-318}$	oral cavity
	GGIA**I**AM$_{78-84}$	*Enterobacteriaceae bacterium 9_2_54FAA*	Uncharacterized protein$_{270-276}$	gut	GGIA**T**AM$_{78-84}$	No homological heptamers in commensal or opportunistic bacteria		
		Eubacterium sulci ATCC 35585	Peptidase, M20/M25/M40 family$_{136-142}$	gut				
		Lactobacillus brevis subsp. gravesensis ATCC 27305	Transporter, major facilitator family protein$_{421-427}$	gut				
	GIA**I**AMA$_{79-85}$	*Lachnospiraceae bacterium 10-1*	Uncharacterized protein$_{148-154}$	gut	GIA**T**AMA$_{79-85}$	*Enterobacter aerogenes UCI 48*	Uncharacterized protein$_{320-326}$	gut
	IA**I**AMAC$_{80-86}$	No homological heptamers in commensal or opportunistic bacteria			IA**T**AMAC$_{80-86}$	No homological heptamers in commensal or opportunistic bacteria		
	A**I**AMACL$_{81-87}$	No homological heptamers in commensal or opportunistic bacteria			A**T**AMACL$_{81-87}$	*Lactobacillus paracasei subsp. paracasei CNCM I-4649*	Class II aldolase/adducin family protein$_{101-107}$	oral cavity, gut
	IAMACLV$_{82-88}$	No homological heptamers in commensal or opportunistic bacteria			**T**AMACLV$_{82-88}$	No homological heptamers in commensal or opportunistic bacteria		

Nucleocapsid protein

Two mutations are known in the Delta variant nucleocapsid (N) protein, namely $R_{203}M$ and $D_{377}Y$ [11].

N protein Delta variant 419 aa

MSDNGPQNQRNAPRITFGGPSDSTGSNQNGERSGARSKQR
RPQGLPNNTASWFTALTQHGKEDLKFPRGQGVPINTNS
SPDDQIGYYRRATRRIRGGDGKMKDLSPRWYFYYLGTG
PEAGLPYGANKDGIIWVATEGALNTPKDHIGTRNPANNA
AIVLQLPQGTTLPKGFYAEGSRGGSQASSRSSSRSRNS
SRNSTPGSSMGTSPARMAGNGGDAALALLLLDRLNQL
ESKMSGKGQQQQGQTVTKKSAAEASKKPRQKRTATKA
YNVTQAFGRRGPEQTQGNFGDQELIRQGTDYKHWPQI
AQFAPSASAFFGMSRIGMEVTPSGTWLTYTGAIKLDDK
DPNFKDQVILLNKHIDAYKTFPPTEPKKDKKKAYETQA
LPQRQKKQQTVTLLPAADLDDFSKQLQQSMSSADSTQA

The heptamers of N protein homologous with the proteins of some opportunistic bacteria and the most common cereals are listed in Table 7.

Table 7

The heptamers of N protein homologous with the proteins of some opportunistic bacteria and the most common cereals

Mutation	Wuhan-Hu				Delta			
	N protein heptamer	Species	Homologous protein heptamer	Localization in the human body	N protein heptamer	Species	Homologous protein heptamer	Localization in the human body
$R_{203}M$	STPGSSR$_{197-203}$	*Prevotella buccalis ATCC 35310*	NHL repeat protein$_{306-312}$	oral cavity	STPGSSM$_{197-203}$	No bacterial or cereal sample		
	TPGSSRG$_{198-204}$	No bacterial or cereal sample			TPGSSMG$_{198-204}$	*Bacteroides uniformis CAG:3*	Uncharacterized protein$_{128-134}$	gut
	PGSSRGT$_{199-205}$	*Zea mays*	Putative WRKY DNA-binding domain superfamily protein$_{78-84}$	gut	PGSSMGT$_{199-205}$	*Oryza sativa subsp. indica*	Putative uncharacterized protein$_{558-564}$	gut
		Sorghum bicolor	Putative uncharacterized protein Sb07g002490$_{27-33}$	gut				
	GSSRGTS$_{200-206}$	*Sorghum bicolor*	Putative uncharacterized protein Sb08g014350$_{176-182}$	gut	GSSMGTS$_{200-206}$	*Fusobacterium sp. CM21*	Permease family protein$_{294-300}$	oral cavity
	SSRGTSP$_{201-207}$	*Hordeum vulgare var. distichum*	Uncharacterized protein$_{267-273}$	gut	SSMGTSP$_{201-207}$	No bacterial or cereal sample		
		Oryza sativa subsp. japonica	Expressed protein$_{216-222}$	gut				
	SRGTSPA$_{202-208}$	No bacterial or cereal sample			SMGTSPA$_{202-208}$	No bacterial or cereal sample		
	RGTSPAR$_{203-209}$	*Oryza sativa subsp. japonica*	Os06g0523800 protein$_{118-124}$	gut	MGTSPAR$_{203-209}$	No bacterial or cereal sample		
$D_{377}Y$	DKKKKAD$_{371-377}$	*Prevotella sp. oral taxon 473 str. F0040*	Pseudouridine synthase, RluA family$_{295-301}$	oral cavity	DKKKKAY$_{371-377}$	*Lachnospiraceae bacterium 3-1*	Oligoendopeptidase F$_{439-445}$	gut
	KKKKADE$_{372-377}$	*Prevotella sp. oral taxon 473 str. F0040*	Pseudouridine synthase, RluA family$_{296-302}$	oral cavity	KKKKAYE$_{372-377}$	*Oryza sativa subsp. indica*	Putative uncharacterized protein$_{1090-1096}$	gut
		Enterococcus faecalis	Uncharacterized protein$_{396-402}$	gut				
	KKKADET$_{373-379}$	No significant sample			KKKAYET$_{373-379}$	*Bacillus infantis NRRL B-14911*	GntR family transcriptional regulator$_{2-8}$	?
	KKADETQ$_{374-380}$	No bacterial or cereal sample			KKAYETQ$_{374-380}$	No bacterial or cereal sample		
	KADETQA$_{375-381}$	*Homo sapiens*	Myopalladin$_{90-96}$	?	KAYETQA$_{375-381}$	No bacterial or cereal sample		
	ADETQAL$_{376-382}$	*Oryza glaberrima*	Uncharacterized protein (Fragment)$_{474-480}$	gut	AYETQAL$_{376-382}$	*Lachnospiraceae bacterium M18-1*	Uncharacterized protein$_{244-250}$	gut
	DETQALP$_{377-383}$	No bacterial or cereal sample			YETQALP$_{377-383}$	*Lachnospiraceae bacterium M18-1*	Uncharacterized protein$_{245-251}$	gut

As shown above, some of the mutations that occurred in the Delta variant increased the homology of its structural proteins with those of the opportunistic and some other bacteria. These data are summarized in Table 8.

Information about the effects that mutations in SARS CoV-2 Delta variant have on the homology between its structural proteins and human opportunistic bacteria proteins are summarized in Figure 1.

DISCUSSION

In Wunan-Hu variant, the S protein molecule contains dozens of heptamers homologous to human proteins. Their total length is 169 amino acid residues, or 13.3% of the S protein molecule total length [5]. For the sake of brevity, we suggest calling **ho**mologous **mot**ifs *homots*. For example, a SARS CoV-2 S protein human homot means a motif common for the S protein and any human protein. The same way "in SARS CoV-2 S protein, the motif SPRRARS is a human homot" means that motif SPRRARS is present in the S protein of coronavirus as well as in some human protein. The term *mimics*, proposed by Damoiseaux et al. [12], is close in meaning but less specific.

We assumed that the reason for the special qualities of SARS CoV-2 Delta variant should be sought in the greater homology of its proteins with those of the human body. However, we did not find any significant differences between Wuhan-Hu variant and Delta variant in their homology to human proteins.

Delta variant stays on the nasal mucosal surface significantly longer than Wuhan-Hu variant (14 vs. 8 days) [13].

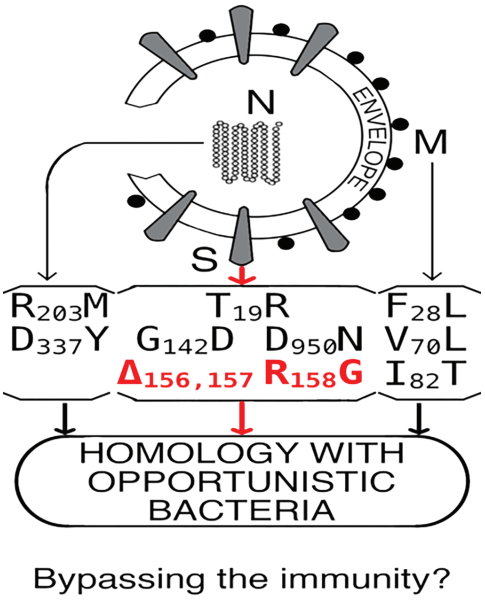

Fig. 1. The effect of mutations in SARS CoV-2 Delta variant structural proteins S, M, and N on their homology with human opportunistic bacteria. The most important mutation, in our opinion, is highlighted in red font

As has been already mentioned, we considered the human proteome in general as a set of proteins synthesized by the macroorganism itself, proteins of commensal and opportunistic bacteria, and the most common digestive proteins, therefore studying the homology of SARS CoV-2 Delta variant with all the listed types of proteins.

Table 8

Mutational changes of homology SARS CoV-2 structural proteins with proteins of opportunistic bacteria and some other functionally significant proteins

Protein	Mutation	Increases homology with proteins of commensal or opportunistic bacteria, inhabitants of the oral cavity, upper respiratory tract or lung	Increases homology with proteins of gut commensal or opportunistic bacteria and/or the most common cereals	Increases homology with some other proteins
S (Table 2)	$T_{19}R$	+	+	
	$G_{142}D^*$	+	–	
	$\Delta_{156,157;}$ $R_{158}G$	**+++**	**+++**	Homology with a protein of *Bacillus sp. NRRL B-14911* that can provoke autoimmune damage to the heart
	$L_{452}R$	–	–	
	$T_{478}K^*$	–	–	
	$P_{681}H$	–	–	
	$D_{950}N^*$	+	+	Homology with a protein of *Human immunodeficiency virus 1* (Table 4)
M (Table 6)	A_2S	–	–	
	$F_{28}L$	+	++	
	$V_{70}L$	++	++	
	$I_{82}T$	+	–	
N (Table 7)	$R_{203}M$	–	–	
	$D_{377}Y$	–	+	

*The same mutation has occurred in Omicron variant.

In S protein, mutations at the positions 19, 142, 156-158, and 950 created a number of heptamers homologous to proteins of bacteria, that are always present in the human nasopharynx, mouth, throat, upper respiratory tract, and lung (Table 2). It is possible that the presence of such homologous motifs allows Delta to bypass the innate immunity protection more successfully.

Mutations S:G_{142}D and S:D_{950}N are also found in Omicron variant, while the mutations S:T_{19}R and S:$\Delta_{156,157}$,R_{158}G are only present in Delta variant. These exclusive Delta variant mutations especially the ones at the positions 156-158 may be the reason for its specific qualities.

The L_{452}R and T_{478}K mutations did not affect the homology of S protein with proteins of opportunistic bacteria (Table 2).

In Delta variant, the positions where the most significant increase in homology occurred — S:$\Delta_{156,157}$;R_{158}G — are located in the N-terminus domain (NTD_{14-303}). So far, researchers have paid less attention to this domain than to the Receptor-binding domain ($RBD_{317-539}$). It is logically consistent to assume that in the S protein molecule one domain is responsible for binding to the receptor and other for structural mimicry and evasion.

The delta variant differs from the other SARS COV-2 variants in 14 positions. According to our data (Fig. 1), six of these alterations involved in the increase in the homology of coronavirus proteins with those of opportunistic bacteria. None of these six alterations are common to the Delta and non-VOC variants. This suggests that the increase in homology with proteins of opportunistic infections is specific to the Delta variant.

We are not yet able to analyze homology data for SARS CoV-2 S protein and the HIV-1 C protein (Table 4).

In M protein, the F_{28}L, V_{70}L, and I_{82}T mutations resulted in the emergence of heptamers homologous to proteins of numerous commensal and opportunistic upper respiratory and gut bacteria (Table 6). M protein is located on the outer side of the virion envelope [5], and these heptamers can participate in immune evasion.

In N protein (Table 7), the mutation N:R_{203}M resulted in the motif $GSSMGTS_{200-206}$ which is homologous to the Permease family $protein_{294-300}$ of *Fusobacterium nucleatum*, an opportunistic periodontal pathogen of the oral cavity [14]. The mutation M:D_{377}Y caused the following effects: (a) disappearance of the heptamer $KADETQA_{375-381}$, homologous to the human protein Myopalladin ($MYPN_{90-96}$), which is involved in communication between the sarcomere and the nucleus in cardiac and skeletal muscles [15]; and (b) emergence of $KKKAYET_{373-379}$, homologous to the heptamer GntR family $transcriptional\ regulator_{2-8}$ *Bacillus infantis*, which is involved in the provocation of immune myocardial disorder [16].

A recent review of the available evidence for immune mechanisms of cardiovascular damage COVID-19 has been presented [17]. N protein, located inside of the virion, should act at the later stages of the infectious process, for example, provoking an autoimmune response.

Of all the Delta variant mutations we studied, none caused an increase in the homology of the SARS CoV-2 S protein with proteins with the most common cereals (Table 3).

Natural selection fixes some substitutions in the primary structure of the protein molecules of viruses and eliminates others. One of the “aims” of selection might be immune evasion. A virus can achieve this by making the most functionally important parts of the protein molecule as similar as possible to the proteins permanently present in the host. Microorganisms, due to their genetic diversity and the huge size of their combined genome, provide more opportunities for viral mimicry than the macroorganism itself. Delta variant has increased homology of S and M proteins with proteins already familiar to human immunity, namely with opportunistic bacteria proteins.

The capacity of SARS CoV-2 for immune evasion can be considered universally acknowledged [3]. Coronavirus and human protein homology may be one of the mechanisms of immune evasion [5]. Delta variant necessarily has structural features that explain its specific qualities. Perhaps the reason is the homology of its proteins with those of commensal bacteria and opportunistic infections of the upper respiratory tract and lung. In this case, the S:$\Delta_{156,157}$;R_{158}G mutation deserves special attention. The reason why SARS CoV-2 Delta variant has these specific qualities, most importantly increased lethality, is most likely to be found in a mutation at positions 156-158 of spike protein. It has not yet been concluded whether the homology of Delta variant proteins with gut bacteria proteins and dietary protein is of any significance.

We hope that this preliminary study will open the door to further research into the immunology and bioinformatics.

METHODS

We used our original way of presenting the text search. The data were obtained from the Uniprot open-access protein database, in which the amino acid sequences of proteins are encoded by a one-letter code. We cut the primary structures of the coronavirus proteins into heptamers using the frameshift method and searched a separate database of 75777 molecules of human proteins [18]. This number is about three times the real number of all human proteins because of repetition and minor differences in the records. We looked for a full match of the 7-mer amino acid sequences in SARS CoV-2 proteins [19] with proteins of other organisms throughout the taxonomic range of evolution from bacteria and plants to humans. Heptamers were chosen as a criterion for homology because of the lack of matches in octamers and tens of thousands of matches in hexamers. In the case of matching heptamers, an alignment was performed on the matching site.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.Т. Марьянович и Д.К. Кормилец написали основной текст рукописи. А.Т. Марьянович и Д.К. Кормилец подготовили анализ данных. Авторы прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Данное исследование представляет собой инициативный проект авторов, финансируемый исключительно из их личных источников.

Заявление о доступности данных. Источником базы данных по 75 777 строкам белков человека является [18]. Источник базы данных объемом ок. 33 млн нитей всех видов белков [19].

Иллюстрации. Для создания наших иллюстраций мы использовали GIMP (версия 2.10.22). Рисунок полностью оригинальный и нигде не публиковался.

ADDITIONAL INFORMATION

Author contributions. A.T. Maryanovich and D.Yu. Kormilets wrote the main manuscript text. A.T. Maryanovich and D.Yu. Kormilets prepared data analysis. The authors read and approved the final version before publication.

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Artwork. We used GIMP (Version 2.10.22) to create our artwork. The figure is completely original and have not been published anywhere.

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DIFFERENCES IN THE ACTIVITY OF AMYLASE, PEPSINOGEN AND LIPASE IN BIOLOGICAL FLUIDS IN PREGNANT WOMEN, DEPENDING ON THE TIMING OF DELIVERY

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Abstract. ***Introduction.*** The issues of enzyme increment of digestive glands have been studied since the sixties of the last century to the present. Enzymes induce the functional activity of secretory glands and prepare the digestive tract of an infant for definitive nutrition through a period of mixed nutrition. ***The purpose of the work*** — to study the sources of enzyme supply of hematrophic, amniotrophic and lactotrophic nutrition of the fetus, the origin of enzymes of amniotic fluid, colostrum and breast milk and their participation in the autolysis of fetal and newborn nutrients. ***Materials and methods***. The material for the study was taken from non-pregnant and pregnant women. The dynamics of changes in the activity of hydrolases in biological fluids was studied. ***Results***. The participation of enzymes secreted in the mother's body in trophosystems during pregnancy and in the postnatal period has been shown. ***Conclusions***. During pregnancy, three systems are distinguished: hematrophic, amniotrophic and lactotrophic with autolytic digestion by increted enzymes.

Keywords: enzymes, incretion, recreation, pregnancy, trophosystem

РАЗЛИЧИЯ АКТИВНОСТИ АМИЛАЗЫ, ПЕПСИНОГЕНА И ЛИПАЗЫ В БИОЛОГИЧЕСКИХ ЖИДКОСТЯХ У БЕРЕМЕННЫХ ЖЕНЩИН В ЗАВИСИМОСТИ ОТ СРОКОВ РОДОРАЗРЕШЕНИЯ

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Резюме. ***Введение.*** Вопросы инкреции ферментов пищеварительных желез изучались с шестидесятых годов прошлого столетия и по настоящее время. Ферменты индуцируют функциональную активность секреторных желез и подготавливают пищеварительный тракт грудного ребенка к дефинитивному питанию через период

смешанного питания. ***Цель исследования*** — изучить источники ферментного обеспечения гематрофного, амниотрофного и лактотрофного питания плода, происхождение ферментов амниотической жидкости, молозива и грудного молока и их участие в аутолизе нутриентов плода и новорожденного. ***Материалы и методы***. Материал для исследования брался у небеременных и беременных женщин. Изучалась динамика изменения активности гидролаз в биологических жидкостях. ***Результаты.*** Показано участие инкретируемых в организме матери ферментов в трофосистемах при беременности и в постнатальный период. ***Выводы.*** Во время беременности выделяются три системы: гематрофная, амниотрофная и лактотрофная с аутолитическим пищеварением инкретируемыми энзимами.

Ключевые слова: ферменты, инкреция, рекреция, беременность, трофосистема

INTRODUCTION

The incretion of digestive glands' enzymes has been studying in the laboratory of Professor G.F. Korotko since the sixties of the last century [6–8]. A biological significance of homeostasis of hydrolases (zymogens and enzymes) in blood was resolved. The diverse role of hydrolases was revealed, including anabolic, regulatory, informational, transport and other functions of pepsinogen, amylase, lipase, alkaline phosphatase in the human body [6, 11, 15].

Experiments on animals have established the nature of the distribution of parenterally administered radiolabeled (J125) enzymes in a mother's body and fetus. Uteroplacental permeability to pepsinogen and amylase, as well as the hydrolytic activity of amniotic fluid, were also studied [3, 13, 14].

In researches on biological fluids, activity of digestive enzymes was studied in blood plasma, urine, and amniotic fluid in women during different stages of pregnancy [1, 6, 7]. After birth, such activity was studied in colostrum and breast milk until the end of breastfeeding [1, 8, 12, 15].

AIM

To study the sources of enzyme support for amniotrophic and lactotrophic nutrition of a fetus. To prove that enzymes are re-secreted in colostrum and breast milk, and that enzymes are used for autolysis of nutrients and induced to their own digestion in gastrointestinal tract of the fetus and newborn.

MATERIALS AND METHODS

Materials for the study were taken from non-pregnant (n=45) and pregnant (n=151) women — women gave birth at different weeks of pregnancy (full-term birth – 86, premature birth — 34, post-term birth — 31).

The dynamics of changes in enzyme activity (pepsinogen, amylase and lipase) in biological fluids (blood, saliva, urine and coprofiltrate, umbilical cord blood and amniotic fluid) were studied at the end of pregnancy, and colostrum and breast milk were studied in the postpartum period.

Determination of proteolytic, amylolytic and lipolytic activities was carried out in blood plasma, saliva, urine and coprofiltrate both in non-pregnant women and pregnant women at the end of pregnancy.

Determination of total proteolytic activity was carried out at pH values of 1.5–2.0 using the spectrophotometric (tyrosine) method of Kunitz–Northrop in modification. Amylolytic activity was determined using Caraway's amyloclastic method. Lipolytic activity was determined using a unified method with olive oil as a substrate [12].

Statistical processing of the obtained data was carried out in Microsoft Excel 2003, Primer of biostatistics 4.03 and SPSS 11.0 programs.

RESULTS

The process of enzyme incretion by digestive glands is reflected in indicators of enzymes' activity in blood and urine, as well as ratios between them [14, 15].

Amylolytic activity in blood plasma of pregnant women is naturally higher than in non-pregnant women, regardless of the timing of delivery (Table 1).

In case of full-term birth, the activity of amylase in urine is almost the same as the control values. In case of preterm and post-term birth, it is reduced, which indicates the retention of the enzyme in the body of pregnant women.

The activity of pepsinogen in blood plasma is more stable than activity of amylase, but excretion of pepsinogen in urine of pregnant women is 2.1 times ($p < 0.001$) higher than in urine of non-pregnant women, indicating the degree of proteolytic enzyme incretion.

Lipolytic activity of blood and urine during pregnancy is increased compared to controls, especially in women with full-term birth.

An example of the re-secreted origin of proteolytic enzymes in saliva is the detection of pepsinogen activity there (Table 2).

Table 1

Indicators of the activity of digestive enzymes in the blood and urine of control group individuals and women at the end of pregnancy with different delivery dates)

Таблица 1

Показатели активности пищеварительных ферментов в крови и моче у лиц контрольной группы и женщин в конце беременности с различными сроками родоразрешения

Показатели / Indicators	Контрольная группа / Control group (n=45)	Срочные роды / Urgent delivery (n=86)	Преждевременные роды / Premature birth (n=34)	Запоздалые роды / Delayed delivery (n=31)
Кровь / Blood				
1. Амилаза (ед/мл) / Amylase (units/ml)	13,5±0,8	25,0±1,3*	22,4±1,3**	20,1±1,4**
2. Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	58,1±1,1	48,2±2,6**	62,3±4,2	60,3±4,4
3. Липаза (ед/мл) / Lipase (units/ml)	18,1±0,7	32,1±1,8*	37,1±1,8*	24,1±1,4
Моча / Urine				
1. Амилаза (ед/мл) / Amylase (units/ml)	64,1±1,6	67,2±2,1	36,2±1,1*	44,3±2,1**
2. Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	4520,3±212,0	9650,1±211,5*	10422,1±231,5*	9309,3±211,5*
3. Липаза (ед/мл) / Lipase (units/ml)	20,6±0,8	41,2±1,9*	30,8±1,9**	31,1±1,7*

Note: the reliability of differences with the indicators of the control group: * — p <0,001; ** — p<0,05.
Примечание: достоверность различий с показателями контрольной группы: * — p <0,001; ** — p <0,05.

Table 2

Indicators of the activity of digestive enzymes in saliva and coprofiltrate of control group individuals and women at the end of pregnancy with different delivery dates

Таблица 2

Показатели активности пищеварительных ферментов в слюне и копрофильтрате у лиц контрольной группы и женщин в конце беременности с различными сроками родоразрешения

Показатели / Indicators	Контрольная группа / Control group (n=45)	Срочные роды / Urgent delivery (n=86)	Преждевременные роды / Premature birth (n=34)	Запоздалые роды / Delayed delivery (n=31)
Слюна / Saliva				
1. Амилаза (ед/мл) / Amylase (units/ml)	2385,3±264,7	4781,6±423,8*	3717,3±223,8**	4702,9±323,8*
2. Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	1520,9±247,6	2612,9±218,1*	2443,5±218,1**	2253,7±118,1**
3. Липаза (ед/мл) / Lipase (units/ml)	64,8±7,0	124,1±11,6*	176,5±11,6*	74,5±3,4**
Копрофильтрат / Coprofiltrate				
1. Амилаза (ед/мл) / Amylase (units/ml)	19,5±0,8	44,4±3,9*	35,2±2,1*	36,2±1,8*
2. Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	442,2±20,5	153,8±10,9*	174,7±16,2*	122,4±8,2*
3. Липаза (ед/мл) / Lipase (units/ml)	320,8±12,6	344,4±17,2	475,3±21,8**	375,3±20,8**

Note: the reliability of differences with the indicators of the control group: * — p <0,001; ** — p <0,05.
Примечание: достоверность различий с показателями контрольной группы: * — p <0,001; ** — p <0,05.

Pepsinogen secreted in stomach is released into saliva from blood, and in pregnant women it is 1.5 times (p<0.001) higher than in non-pregnant women, thereby ensuring the participation of salivary glands in secretion of the enzyme.

The excretory-re-secretory origin of the hydrolytic activity of coprofiltrates is explained by the fact of amylase, pepsinogen and lipase detection in feces [3, 6, 11].

During pregnancy, amylolytic and lipolytic activities increase, and pepsinogen activity decreases almost 3 times (p <0.001). These relationships are inversely dependent on the level of pepsinogen excretion in urine, which generally affects the pepsinogen content in blood of pregnant women.

Another trophic system is associated with fetal amniotrophic nutrition and autolytic digestion due to the absorption of amniotic fluid, which contains both nutrients and enzymes corresponding to substrates — hydrolases of maternal origin [2–4].

This is proven by the presence of amylase, pepsinogen and lipase in amniotic fluid, which has the property of accumulating enzymes used by a fetus for hydrolytic processes in gastrointestinal tract when digestion is still imperfect (Table 3).

Of particular interest are data on the activity of enzymes secreted into colostrum and breast milk of women depending on the delivery time (Table 4).

Colostrum is more active in enzymes than breast milk. General proteolytic (4 times; p <0.001) and lipolytic (3 times; p <0.001) activities differ especially from mature breast milk, while the amylolytic activity of these biological fluids differs by less than 2 times (p <0.05) with a decrease during the transition to mature breast milk. This proves the role of colostrum and breast milk enzymes in colostrum-lactotrophic nutrition.

DISCUSSION

Maternal blood plasma, being the nutrient medium of a fetus, ensures hydrolytic processes and plays a role in anabolic processes [3, 6, 12, 14, 15].

The conducted studies revealed an increase in the activity of amylase and lipase in blood serum of all women at the end of pregnancy, regardless of the time of delivery. Multidirectional changes in this fluid were observed in pepsinogen: a decrease in enzyme activity in women with full-term birth and an increase in post-term and premature birth.

The amylase excretion in urine of pregnant women with full-term birth corresponded to indicators of the control group, and in premature and post-term birth the enzyme activity decreased, which indicates the retention of amylase in the body of pregnant women [1, 3, 6]. The activity of pepsinogen and lipase in urine is increased in port-term pregnancy compared to controls, especially in full-term labour.

Amylolytic activity of saliva is caused not only by the secretion of α-amylase synthesized by the salivary glands, but also by the secreted pancreatic α-amylase. In this regard, the

Table 3

Indicators of the activity of digestive enzymes in amniotic fluid and umbilical cord blood in pregnant women, depending on the timing of delivery

Таблица 3

Показатели активности пищеварительных ферментов в амниотической жидкости и пуповинной крови у беременных в зависимости от сроков родоразрешения

Биологическая жидкость / Biological fluid	Ферменты / Enzymes	Срочные роды / Urgent delivery (n=86)	Преждевременные роды / Premature birth (n=34)	Запоздалые роды / Delayed delivery (n=31)
Амниотическая жидкость / Amniotic fluid	Амилаза (ед/мл) / Amylase (units/ml)	16,3±0,7	27,7±0,9*	25,8±0,9*
	Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	5664,5±225,1	5840,8±204,3	6387,0±249,4**
	Липаза (ед/мл) / Lipase (units/ml)	228,7±18,4	201,4±15,3	234,2±16,2
Пуповинная кровь / Umbilical cord blood	Амилаза (ед/мл) / Amylase (units/ml)	35,3±1,2	10,9±0,8*	15,1±1,1*
	Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	1041,6±88,5	1214,4±97,3**	873,0±65,4
	Липаза (ед/мл) / Lipase (units/ml)	164,9±11,2	190,4±13,4	61,2±4,5*

Note: the reliability of differences with the indicators of the control group: * — p <0,001; ** — p <0,05.
Примечание: достоверность различий с показателями у беременных женщин, родивших в срок: * — p <0,001; ** — p <0,05.

Table 4

Indicators of the activity of digestive enzymes in colostrum and breast milk in lactating women, depending on the timing of their delivery

Таблица 4

Показатели активности пищеварительных ферментов в молозиве и грудном молоке у кормящих женщин в зависимости от сроков их родоразрешения

Биологическая жидкость / Biological fluid	Ферменты / Enzymes	Срочные роды / Urgent delivery (n=86)	Преждевременные роды / Premature birth (n=34)	Запоздалые роды / Delayed delivery (n=31)
Молозиво / Colostrum	Амилаза (ед/мл) / Amylase (units/ml)	401,3±21,7	511,9±32,5**	440,9±20,3
	Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	609,5±26,3	532,4±18,1	581,1±29,4**
	Липаза (ед/мл) / Lipase (units/ml)	634,1±28,5	523,2±25,3**	562,9±23,6**
Грудное молоко / Breast milk	Амилаза (ед/мл) / Amylase (units/ml)	215,3±19,6	267,8±14,5**	233,4±15,6
	Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	152,9±12,1	124,2±10,2	179,1±11,6**
	Липаза (ед/мл) / Lipase (units/ml)	222,2±17,2	285,4±14,7**	230,2±12,7

Note: the reliability of differences with the indicators of the control group: * — p <0,001; ** — p <0,05.
Примечание: достоверность различий с показателями у беременных женщин, родивших в срок: * — p <0,001; ** — p <0,05.

increased amylolytic activity in pregnant women may be due to both amylases [4, 5, 7–10, 13, 14].

All pregnant women showed an increase in the amylase, pepsinogen and lipase activity in saliva, which indicates the released (secreted in saliva) origin of these enzymes.

If the salivary glands do not experience hydrostatic resistance, then in the pancreatic ducts of pregnant women this is greater than in non-pregnant women [1, 3, 6]. Accordingly, the lipolytic activity of saliva also changes, especially in premature birth, which is associated with an increased lipase activity in blood.

By the end of pregnancy, amylolytic and lipolytic activities of the coprofiltrate increased with the greatest changes in women with full-term and premature births. At the same time, there was a decrease in the pepsinogen activity in all studied groups of pregnant women compared with controls.

The amnio-placental barrier is involved in the selective accumulation of digestive enzymes in amniotic fluid, in which enzymes' content is quite significant [2, 3, 12, 15]. Umbilical cord blood is rich in proteolytic and lipolytic enzymes, especially in women with premature birth.

In the postnatal period, a child switches to a colostrum-lactotrophic type of nutrition [1, 3, 12]. In this regard, we found the highest levels of hydrolase activity in colostrum, with a subsequent decrease in its activity in breast milk on the fifth day of life. Incretion, releasing and excretion of enzymes are interrelated, maintaining the constancy of their blood content for the implementation of anabolic and regulatory processes in a fetus [13, 14, 16].

Thus, the data obtained on enzyme homeostasis in the "mother-fetus-newborn" system serve as additional material on trophic systems with their autolytic type of digestion. In the antenatal period, histotrophic, hematotrophic (transplacental) and amniotrophic nutritions are organized, and in the postnatal period, there is a lactotrophic nutrition. Enzymes induce the functional activity of the secretory glands and prepare the infant's digestive system for definitive nutrition through a period of mixed feeding.

CONCLUSION

1. Amylolytic activity of blood serum, urine and saliva in pregnant women is naturally higher than in non-pregnant women, regardless of the time of delivery.

2. The activity of pepsinogen and lipase in blood, urine and saliva during pregnancy is increased compared to the controls, especially in women with full-term delivery.

3. In coprofiltrate, an increase in amylase and lipase activity was observed, but a decrease in pepsinogen was observed in all pregnant women studied by the end of pregnancy.

4. Amniotic fluid and umbilical cord blood are rich in proteolytic and lipolytic enzymes with the greatest changes in women with premature and post-term birththe the.

5. Hydrolytic activity of colostrum is significantly higher than that of breast milk on the fifth day of life

6. Enzymes participate in autolytic digestion and induce the infant's own digestion in the body.

ADDITIONAL INFORMATION

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

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

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

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SEXUAL CHARACTERISTICS OF INTERCORTICAL RELATIONSHIPS IN THE DELTA RANGE OF THE POWER SPECTRUM WHEN PERFORMING ARBITRARY BIMANUAL PURPOSEFUL MOVEMENTS

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Abstract. The level of bimanual coordination in men and women is represented by different effectiveness, which is explained by the peculiarities of the organization of the sensorimotor sphere in women and men. The processes of excitation and inhibition are complementary and contribute to the effective construction of the motor system. The aim of the study is to study the sexual characteristics of cortical activation in the delta range and to identify intersystem cortical relationships in the implementation of complexly coordinated bimanual movements. The level of brain activity was assessed by recording the delta rhythm during electroencephalography, and the results of the coordination index using the method of supportmetry. Significant differences in the inhibitory activity of the cerebral cortex and the functional relationships of its centers have been revealed, which causes differences in the resulting effectiveness of motor programs. In the female group, high activity in the delta range of the left frontal associative cortex and a pronounced connection between the occipital and premotor regions on the right are of leading importance in the formation of the motor program. In men, hemispheric asymmetry with inhibition of the right hemisphere contributes to a more perfect result.

Keywords: voluntary motor activity, electroencephalography, bimanual coordination, cortical activity

ПОЛОВЫЕ ОСОБЕННОСТИ МЕЖКОРКОВЫХ СВЯЗЕЙ В ДЕЛЬТА-ДИАПАЗОНЕ СПЕКТРА МОЩНОСТИ ПРИ ВЫПОЛНЕНИИ ПРОИЗВОЛЬНЫХ БИМАНУАЛЬНЫХ ЦЕЛЕНАПРАВЛЕННЫХ ДВИЖЕНИЙ

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Резюме. Уровень бимануальной координации у лиц мужского и женского полов представлен разной результативностью, что объясняется особенностями организации сенсомоторной сферы у женщин и мужчин. Процессы возбуждения и торможения являются взаимодополняющими и способствуют эффективному построению двигательной системы. Целью исследования является изучение половых особенностей активации коры в дельта-диапазоне и выявление внутрисистемных корковых взаимосвязей при реализации

сложноскоординированных бимануальных движений. Уровень активности мозга оценивался регистрацией дельта-ритма при проведении электроэнцефалографии, а результаты показателя координации — с помощью метода суппортметрии. Выявлены достоверные различия в тормозной активности коры больших полушарий и функциональных взаимосвязях ее центров, что обусловливает различия результирующей эффективности выполнения моторных программ. В женской группе ведущее значение в формировании моторной программы имеет высокая активность в дельта-диапазоне левой фронтальной ассоциативной коры и выраженная связь затылочной и премоторной области справа. У мужчин межполушарная асимметрия с торможением правого полушария способствует более совершенному результату.

Ключевые слова: произвольная двигательная активность, электроэнцефалография, бимануальная координация, корковая активность

INTRODUCTION

Sex differences in motor functioning do not cause doubts among modern researchers [1, 5, 8, 11, 15], but the nature of these differences is still insufficiently studied. Rhythmic bimanual movements are represented in the central nervous system as a motor program of their tact, within which a strategy of locomotion execution is formed [10, 12]. Activity of various centers of cerebral hemispheric cortex and their interrelation are a leading factor in initiating and correcting engrams of movements [3, 5, 7, 15]. Excitation and inhibition processes are complementary and contribute to effective construction of a motor system [1, 9, 16]. A commonly accepted technique for recording the electrical activity of the brain — electroencephalography — makes it possible to record slow waves in a delta-band and assess inhibition of cortical areas of large hemispheres [4].

AIM

The aim is to examine sex-specific features of cortical activation in the delta band and to identify intrasystem cortical interconnections in realizing coordinated complex bimanual movements.

MATERIALS AND METHODS

The research was conducted in the laboratory of physiology of motor activity of the Research Institute of Physiology, united with the single-profile department of the Federal State Budgetary Educational Institution of Higher Professional Education “Kursk State Medical University” of the Ministry of Health of Russia.

53 men and 51 women aged 18 to 24 years took part in the experiment on the basis of informed voluntary consent. Participants had to undergo an assessment of bimanual coordination by means of suportmetry [10]. As part of this method, participants had to perform four tasks of varying difficulty; the results were used to evaluate time required to perform a task, number of errors, time spent in and out of the task contour, as well as to calculate an integral index of coordination. Then, after completing the tasks, electroencephalogram was recorded for 2 minutes. A «10–20» international system of electrodes was used for recording, within which activity from 21 calyx electrodes was recorded. The data obtained from electrodes Fp1-A1, Fp2-A2, C4-A2, C3-A1, T3-A1, T4-A2, O1-A1, O2-A2 were used, since these electrodes reflect activity of main cortical areas responsible for movements.

Electrode impedance did not exceed 20 kOhm, sensitivity was established at 7 μV/mm. Further computer processing of a signal was carried out by the fast Fourier transform method, with no fewer than 30 epochs of 2 s averaging [4, 6].

An electroencephalograph-analyzer EEGA-21/26 “Encephalan-131–03” (Taganrog, Russia) was used in the experiment. Statistical processing was performed by comparing mean values of a power spectrum in two groups. Quantitative indices were evaluated for conformity to normal distribution using the Kolmogorov-Smirnov criterion (when the number of subjects was more than 50). If there was no normal distribution, quantitative data were described using median (Me), lower and upper quartiles (Q1–Q3). Categorical data were described with absolute values and percentages [2].

RESULTS

The lowest values were recorded in C3-A1 leads when comparing the parameters in delta range (Table 1) in women. Values in T3-A1 were higher by 13%, in Fp1-A1 by 29%, in T4-A2 by 51%, in O2-A2 by 67%, and in Fp2-A2 by 79%. Mean values in O1-A1 are 9% higher than the median in C3-A1 and 63% higher in C4-A2. The highest value is in Fp2-A2. The lowest value of the power spectrum in men was registered in C3-A1. The values in T3-A1 are higher by

Table 1

The average values of the EEG power spectrum in the delta range in women and men when performing arbitrary bimanual purposeful movements

Таблица 1

Средние показатели спектра мощности ЭЭГ в дельта-диапазоне у женщин и мужчин при выполнении произвольных бимануальных целенаправленных движений

Группа / Group	Отведение энцефалограммы / Electroencephalogram leads							
	Fp1-A1	Fp2-A2	C3-A1	C4-A2	O1-A1	O2-A2	T3-A1	T4-A2
Женщины / Women	8,31 (Me)	11,56 (Me)	6,45 (Me)	10,49±9,73 (M±SD)	7,03±3,93 (M±SD)	10,80 (Me)	7,28 (Me)	9,72 (Me)
Мужчины / Men	9,43 (Me)	11,83 (Me)	8,62 (Me)	11,36±7,54 (M±SD)	10,85±6,46 (M±SD)	13,58 (Me)	8,68 (Me)	9,95 (Me)

Note: M — the average value; SD — the standard deviation; Me — the median.
Примечание: M — среднее значение; SD — стандартное отклонение; Me – медиана.

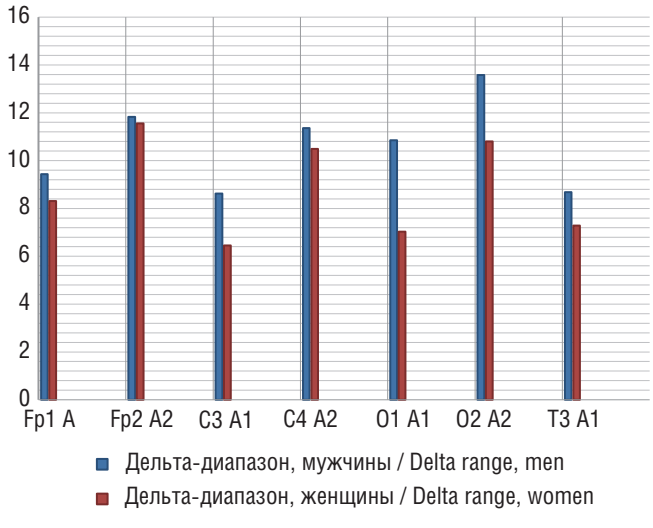

Fig. 1. Comparative characteristics of the average values of the EEG power spectrum in the delta range in women and men when performing arbitrary bimanual purposeful movements

Рис. 1. Сравнительная характеристика средних показателей спектра мощности ЭЭГ в дельта-диапазоне у женщин и мужчин при выполнении произвольных бимануальных целенаправленных движений

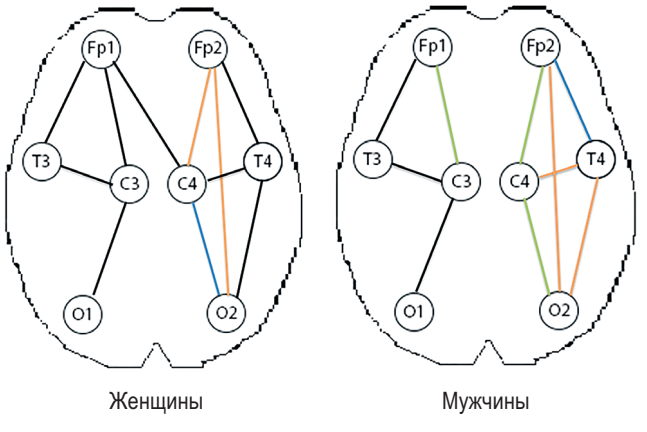

Fig. 2. Correlation pleiades of the power spectrum of female and male subjects in the delta range when performing arbitrary bimanual purposeful movements

Рис. 2. Корреляционные плеяды спектра мощности испытуемых женского и мужского пола в дельта-диапазоне при выполнении произвольных бимануальных целенаправленных движений

1%, by 9% in Fp1-A1, by 15% in T4-A2, by 37% in Fp2-A2, and by 56% in O2-A2. Mean value in C4-A2 is 26% higher than median in O1-A1, and 32% higher in C3-A1. The maximum value was detected in O2-A2, indicating high delta activity in the occipital lobe on the right side.

Comparative analysis of mean values female and male groups (Fig. 1) showed that Fp1-A1 reflects left frontal lobe activity. Values in the male study group were 13% ($p < 0.001$) higher than in the female group. Fp2-A2, showing functioning of the right frontal lobe, were 2% ($p < 0.001$) higher in males. C3-A1 (projection of the central premotor cortex on the left) is 34% higher ($p < 0.001$). C4-A2 which is the projection of the central premotor cortex on the right, is 8% higher ($p < 0.001$). O1-A1 shows functioning of the left occipital region, and appears to be higher by 54% ($p < 0.001$). O2-A2 (the right occipital region) is higher by 26%, T3-A1, the left temporal region projection, is higher by 19%, and T4-A2, the right temporal region projection, is higher by 2% ($p < 0.001$). Comparative analysis of a power spectrum in delta-band revealed predominance of brain activity in all areas in males compared to females.

When conducting correlation analysis between brain activity indices in delta-band of a power spectrum in males, the absence of interconnections between left and right hemi-

spheres is observed (Fig. 2). At the same time, the density of connections is higher in right brain areas. In women, the connection between the right and left hemispheres is provided by interaction between the left frontal cortex on the left and the central premotor cortex on the right. At the same time, the connection strength in male group in Fp2-A2 — C4-A2 is 15% higher ($p < 0.001$), in T4-A2 — O2-A2 is 17% higher ($p < 0.001$), in Fp1-A1 — C3-A1 is 34% higher ($p < 0.001$), in Fp2-A2 — T4-A2 is 34% higher ($p < 0.001$). C4-A2 — O2-A2 was 14% higher in women ($p < 0.001$). The central premotor area on the right side is the multipolar center, it has the highest value of a total correlation coefficient in women. Similarly, it has bilateral correlations of high density together with the occipital region on the right side. Central premotor cortex on the right is also the area of high correlation with the maximum value of a total coefficient in men. However, correlations of high density are located between the frontal associative cortex on the right and the right temporal area.

DISCUSSION

The delta rhythm has a thalamocortical nature [4], and indicates inhibitory activity of specific thalamic nuclei due to mirror neurons located in the cortex [9], reflecting processes of memory consolidation and cognitive activity [7, 15, 17]. Since motor activity is a combination of excitation and inhibition processes, this rhythm will have a significant effect on implementing motor programs [1, 9, 16]. Maximum activity in the left frontal lobe in women can indicate deep inhibition processes of tertiary motor fields of the associative cortex on the left. At the same time, a bridge between the left and right hemispheres, which is located between the left frontal lobe and the central premotor cortex, may account for lower indicators of bimanual coordination in women compared to men. The pronounced association between occipital and central premotor areas on the right may have an inhibitory effect on retrieval processes of existing engrams from memory.

The male group is characterized by higher delta-band activity in all electrodes, indicating a deeper inhibition of structures. Mapping of functional connections in this group allows us to suggest the absence of mutual influences between the hemispheres and a pronounced right-sided asymmetry of activity. The bilateral connection of high density between frontal and temporal lobes on the right can speak about mutual inhibition of tertiary motor fields of frontal associative cortex and vestibular centers on the right. Thus, under the conditions of suportmetry tasks performance, it has a positive influence on a better result.

Bimanual coordination indices have significant differences in women and men, thus confirming previously obtained data [11, 13]. Results differ due to distinctions in tactics during task performance. Thus, there are differences in initiation and correction of motor programs in cortex [12, 14]. Registration of delta brain activity allows us to evaluate inhibition of centers involved in movement. The female group is characterized by active inhibition of the left frontal associative cortex, the presence of a “bridge” linking the hemispheres in the left frontal and right central premotor areas, and pronounced connections between the central premotor and occipital cortex on the right side, which together shows a less effective strategy for performing a motor act compared to men. Delta activity is more pronounced in men and indicates deeper inhibition in all cortical centers. The absence of connections between hemispheres with pronounced right-sided asymmetry of activity and mutual suppression of temporal and frontal areas on the right reflects a more efficient process of bimanual coordination.

CONCLUSION

1. Women and men revealed different strategies for performing arbitrary bimanual goal-directed movements.

2. Females have high activity in the delta-band of the left frontal associative cortex and pronounced association of the occipital and premotor areas on the right side which influences the formation of motor programs.

3. Interhemispheric asymmetry in men inhibits the right hemisphere and contributes to a better motor functioning.

ADDITIONAL INFORMATION

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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RISK FACTORS FOR ADVERSE OUTCOMES OF COVID-19 PNEUMONIA IN PATIENTS INTENSIVE CARE UNIT WITH COMORBID DISEASES

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Abstract. ***Introduction.*** The main risk factors for adverse outcomes in patients with COVID-19 pneumonia are age and comorbidities. For accurate risk stratification, a comprehensive dynamic assessment of clinical, laboratory, and hemodynamic factors of patients is important. ***The aim of the study*** was to assess the risk factors for the development of a lethal outcome in patients with COVID-19 pneumonia with comorbid diseases based on the analysis of time trends in clinical and laboratory characteristics. ***Materials and methods.*** A retrospective observational, multicenter study of 125 patients aged 18 to 75 years with laboratory-confirmed COVID-19 and/or ICD-10 U07.1 hospitalized with acute respiratory failure was conducted from March 2020 to May 2022. Demographic, clinical, and laboratory data of patients were recorded at the time of hospitalization and during the first 5 days of treatment. ***Results.*** In the analysis of operational characteristics and Kaplan–Meier survival curves, the age of patients >71 years, body mass index >29.8 kg/m^2, and D-dimer levels >1600 ng/mL and procalcitonin >3.4 ng/mL were statistically significantly associated with the risk of death. For two parameters (D-dimer and procalcitonin levels), the prognostic value of the temporal trend was statistically significantly higher compared to their daily values. ***Conclusion.*** The increased risk of death in patients with COVID-19 pneumonia and comorbid diseases is associated with older age and high body mass index, but not with comorbid diseases. Temporal trends in D-dimer and procalcitonin have a greater predictive value compared to their daily values.

Keywords: COVID-19, pneumonia, comorbid diseases, risk of death, temporal trends

ФАКТОРЫ РИСКА НЕБЛАГОПРИЯТНЫХ ИСХОДОВ COVID-19 ПНЕВМОНИИ У ПАЦИЕНТОВ ОТДЕЛЕНИЙ ИНТЕНСИВНОЙ ТЕРАПИИ С КОМОРБИДНЫМИ ЗАБОЛЕВАНИЯМИ

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Резюме. ***Введение.*** Основными факторами риска неблагоприятных исходов у пациентов с COVID-19 пневмонией являются возраст и коморбидные заболевания. Для точной стратификации риска важна комплексная

динамическая оценка клинических, лабораторных и гемодинамических факторов пациентов. ***Цель исследования*** — оценка факторов риска развития летального исхода у пациентов с COVID-пневмонией с коморбидными заболеваниями на основе анализа временных трендов клинико-лабораторных характеристик. ***Материалы и методы.*** Ретроспективное обсервационное мультицентровое исследование 125 пациентов в возрасте от 18 до 75 лет с лабораторно подтвержденным COVID-19 и/или с диагнозом U07.1 по МКБ-10, госпитализированных с острой дыхательной недостаточностью, было проведено с марта 2020 г. по май 2022 г. Критерий невключения — рефрактерный септический шок. Демографические, клинические и лабораторные данные пациентов были записаны на момент госпитализации и в первые 5 суток лечения. ***Результаты***. При анализе операционных характеристик и кривых выживаемости Каплана–Мейера возраст пациентов >71 года, индекс массы тела >29,8 кг/м^2 и уровни D-димера >1600 нг/мл и прокальцитонина >3,4 нг/мл были статистически значимо связаны с риском смерти. Для двух параметров (уровни D-димера и прокальцитонина) прогностическая величина временного тренда была статистически значимо выше в сравнении с их суточными значениями. ***Заключение.*** Увеличение риска смерти пациентов с COVID-19 пневмонией и коморбидными заболеваниями связано с пожилым возрастом и высоким индексом массы тела, но не с коморбидными заболеваниями. Временные тренды D-димера и прокальцитонина обладают большей прогностической ценностью в сравнении с их суточными значениями.

Ключевые слова: COVID-19, пневмония, коморбидные заболевания, риск смерти, временные тренды

INTRODUCTION

Main factors that contribute to risks of severe morbidity and mortality in patients with COVID-19 and COVID-19-induced pneumonia, in addition to age, are comorbid diseases such as arterial hypertension, diabetes mellitus, overweight and others [1–3, 6–9, 20].

Several large multicenter trials have examined clinical and laboratory characteristics of patients when they were admitted to an intensive care unit (ICU), where several serum biomarkers predicted adverse outcome, including elevated levels of interleukin-6, ferritin, C-reactive protein, lactate dehydrogenase, D-dimer, and fibrinogen, as well as reduced levels of antithrombin and lymphopenia [1, 5, 10, 12, 20]. A comprehensive dynamic assessment of patients' clinical, laboratory, and hemodynamic factors is important for risk stratification when implementing COVID-19 pneumonia treatment protocols. Since patients with COVID-19 pneumonia and comorbid diseases require prolonged respiratory support in ICU, the use of time trends of clinical and laboratory characteristics has been proposed to estimate survival prognosis more accurately [14].

AIM

The aim of was to evaluate risk factors for lethal outcome in ICU patients with COVID-19 pneumonia with comorbid diseases based on time trend analysis of clinical and laboratory characteristics.

MATERIALS AND METHODS

Design — a retrospective observational multicenter research was conducted on the basis of the Republican Clinical Infectious Diseases Hospital and Clinical Emergency Hospital (Ufa, Republic of Bashkortostan) from March 2020 to May 2022. The trial consecutively enrolled 130 patients aged 18 to 75 years with laboratory-confirmed COVID-19 and/or a diagnosis of U07.1 (ICD-10 (highly suspected on clinical grounds and/or confirmed by a positive real-time polymerase chain reaction with reverse transcriptase (PCR test) in nasal and pharyngeal swabs or lower respiratory tract aspirate), hospitalized in ICU with acute respiratory failure (blood oxygen saturation (SpO_2) <90% with room air or <95% with inhalation of 2 L of oxygen through nasal cannulas) for respiratory support. Criteria for non-inclusion were refractory septic shock, defined as requiring a dose of norepinephrine or equivalent above >0.1 mcg/kg per minute or the use of two or more vasopressors.

Patients' clinical data (respiratory support parameters: high-flow oxygen therapy, non-invasive and artificial lung ventilation (NIV and ALV); respiratory parameters: fraction of inhaled oxygen (FiO_2), SpO_2/FiO_2 ratio; medications: antiviral, immunomodulatory and vasoactive drugs, antibiotics, corticosteroids) were recorded in the ProMed medical information system at the time of hospitalization and then daily during the first 5 days of treatment. Patients were treated according to temporary methodological recommendations of the Russian Ministry of Health that were relevant for the period of hospitalization.

Patients who died in the first 24 hours after admission were excluded (n=5), thus 125 patients were included in the final analysis. 110 (88.0%) patients had positive PCR test results. Comorbid disease characteristics of patients with COVID-19 pneumonia are summarized in Table 1. At least 1 disease was reported in 29 patients, most commonly obesity (44.8%) or arterial hypertension (24.1%). The remaining patients had 2 to 7 (total 217) diseases, with an average of 2.26 diseases per patient. Arterial hypertension was the most common comorbid disease (54.4%), followed by heart disease (34.4%), obesity (35.2%), and diabetes mellitus (21.6%). Arterial hypertension was associated with the highest number of comorbid conditions, most commonly heart disease (33.6%), obesity, and diabetes mellitus (equally 18.1% each). Heart disease was legitimately most often accompanied by obesity (15.5%) and cardiac arrhythmia (14.6%). Obesity and diabetes mellitus were found in 9.5% of cases of comorbid diseases.

Statistical data processing was performed by using MedCalc software package (v 11.3.1.0, Belgium) in accordance with recommendations for processing results of biomedical studies. Continuous variables were presented as median and 25–75% interquartile range, categorized variables were presented as absolute values and relative frequency. Comparison of results between patient groups was performed using the Mann-Whitney U-test for nonparametric variables and Pearson's χ^2 test or Fisher's exact test for corresponding categorized variables. Kaplan-Meier survival estimates were calculated and a log-rank test was used to compare groups by survival.

RESULTS

Main vital signs and treatment modalities were monitored at the onset of the disease (Table 2).

Median duration of fever in surviving patients was 12.6 (7.8–14.5) days, and cough persisted for 17.9 (13.0–25.6) days (Figure 1). The median time from disease onset to onset of dyspnea was similar in surviving and deceased patients, with a median duration of 14.2 (8.6–17.6) days in surviving patients. Median time from onset to tracheal intubation and ventilator was 17.5 (11.9–21.0) days. Median time from dyspnea to ventilator was 7.0 (3.0–9.5) days. Median duration of respiratory support was 5 (3–19) days ranging from 1 to 70 days. Median duration of hospitalization in ICU was 7.5 (3.5–15.6) days for deceased patients and 9.4 (4.7–24.0) days for surviving patients, ranging from 3 to 73 days. Median length of hospitalization was 19.5 (10.8–44.5) days with a range of 1 to 96 days. Median time from onset to hospital discharge was 25.6 (15.2–36.0) days, and median time to death was 19.6 (9.1–30.1) days. Cumulative follow-up time from hospitalization to transfer from ICU or death was 2655 days with a median of 22.1 (11.3–32.9 days) patient-days with a range of 4 to 50 days.

A comparative analysis of main symptoms of the disease course and treatment tactics in surviving and deceased patients is presented in Figure 1.

At the time of admission to ICU, the SpO_2/FiO_2 ratio was 118.0% (63.1–172.8), and all patients required respiratory support. 65.6% of patients required high-flow oxygen therapy or NILV. Among 46 patients who required ventilator support, 38 patients eventually died. Patients initially

Table 1

Comorbid diseases of patients with COVID-19 pneumonia

Таблица 1

Коморбидные заболевания пациентов с COVID-19 пневмонией

Характеристики / Characteristics	Значения / Values
Артериальная гипертензия / Arterial hypertension, n (%)	68 (54,4)
Сахарный диабет / Diabetes mellitus, n (%)	27 (21,6)
Ожирение / Obesity, n (%)	44 (35,2)
Сердечная аритмия / Cardiac arrhythmia, n (%)	18 (14,4)
Заболевания сердца / Heart diseases, n (%)	43 (34,4)
Заболевания легких / Lung diseases, n (%)	20 (16,0)
Заболевания почек / Kidney diseases, n (%)/	9 (7,2)
Заболевания печени / Liver diseases, n (%)	12 (9,6)
Злокачественные новообразования / Malignant neoplasms, n (%)	8 (6,4)
Индекс Чарльсона, баллы / Charleson Index, points	3,1 (1,6–4,8)
Индекс Чарльсона >3 баллов / Charleson Index >3 points, n (%)	45 (36,0)

Table 2

Demographic and clinical characteristics of stratified groups of patients with COVID-19 pneumonia

Таблица 2

Демографические и клинические характеристики стратифицированных групп пациентов с COVID-19 пневмонией

Характеристики / Characteristics	Выжившие / Survival (n=55)	Умершие / Dead (n=70)	p
Пациенты / Patients, n	55	70	–
Возраст, лет / Age, years	63,0 (48,7–76,4)	72,1 (57,7–81,4)	0,001
Мужчины / Men, n (%)	27 (49,1)	37 (52,9)	Нд / Ud
ИМТ кг/м^2 / BMI, kg/m^2	29,1 (23,4–34,8)	27,1 (22,2–32,0)	0,037
Одышка / Dyspnea, n (%)	52 (94,5)	65 (92,8)	Нд / Ud
Кашель / Cough, n (%)	52 (94,5)	67 (95,7)	Нд / Ud
Лихорадка / Fever, n (%)	50 (90,9)	67 (95,7)	Нд / Ud
Площадь поражения легких начальная / Initial area of lung damage, %	39,3 (19,3–59,3)	46,8 (21,8–71,8)	Нд / Ud
Площадь поражения легких / Final area of lung damage, %	64,9 (47,1–82,7)	62,0 (41,7–82,3)	Нд / Ud
Положительный ПЦР-тест / Positive PCR test, n (%)	52 (94,5)	58 (82,9)	0,048
Медикаменты / Medicines, n (%)			
Противовирусные / Antiviral	47 (85,5)	54 (77,1)	Нд / Ud
Моноклональные антитела / Monoclonal antibodies	13 (23,6)	20 (26,7)	Нд / Ud
Глюкокортикостероиды / Glucocorticosteroids	55 (100,0)	62 (88,6)	0,010
Мочегонные / Diuretics	31 (56,4)	40 (57,1)	Нд / Ud
Антикоагулянты / Anticoagulants	51 (92,7)	67 (89,3)	Нд / Ud
Гипотензивные / Hypotensive	32 (58,2)	45 (64,3)	Нд / Ud
Антибиотики / Antibiotics	55 (100,0)	61 (87,1)	0,006
Лечебные мероприятия, n (%)			
Респираторная поддержка / Respiratory support	47 (85,4)	35 (50,0)	0,001
ИВЛ / MV	8 (14,5)	35 (50,0)	0,001
Вазопрессорная поддержка / Vasopressor support	19 (34,5)	21 (28,0)	Нд / Ud
Нутритивная поддержка / Nutritional support	31 (56,4)	52 (69,3)	Нд / Ud

Note: Ud — unreliable differences; BMI — body mass index; MV — mechanical ventilation; PCR — polymerase chain reaction.
Примечание: ИВЛ — искусственная вентиляция легких; ИМТ — индекс массы тела; нд — недостоверные отличия; ПЦР — полимеразная цепная реакция.

receiving respiratory support in the form of non-invasive lung ventilation had a statistically significant lower risk of death than patients initially receiving ventilator support: relative risk (RR) 0.82; 95% CI 0.72–0.95; p=0.010. Patients who initially received respiratory support by NILV followed by a switch to ventilator had a statistically significant higher risk of death compared to patients whose respiratory support was limited to NILV: OR 1.49; 95% CI 1.23–1.78; p=0.010. The mortality of patients with subsequent ventilator support was similar to patients who received ventilator support from the beginning of hospitalization: OR 1.18; 95% CI 0.75–1.33; p=0.120. 80.8% of patients received antiviral drugs, 92.8% of patients received antibiotic therapy, 26.4% of patients received monoclonal antibodies, and 93.6% of patients received corticosteroids. Time median from onset of illness to treatment was 9.9 (82–17.4) days for surviving patients receiving antiviral drugs.

Table 3 presents time trends consisting of 23 parameters over the course of hospitalization in stratified patient groups.

Baseline lymphocyte levels were roughly equal in surviving and deceased patients at onset; surviving patients had the lowest lymphocyte levels on day 7–8 after onset and returned to normal during hospitalization, whereas

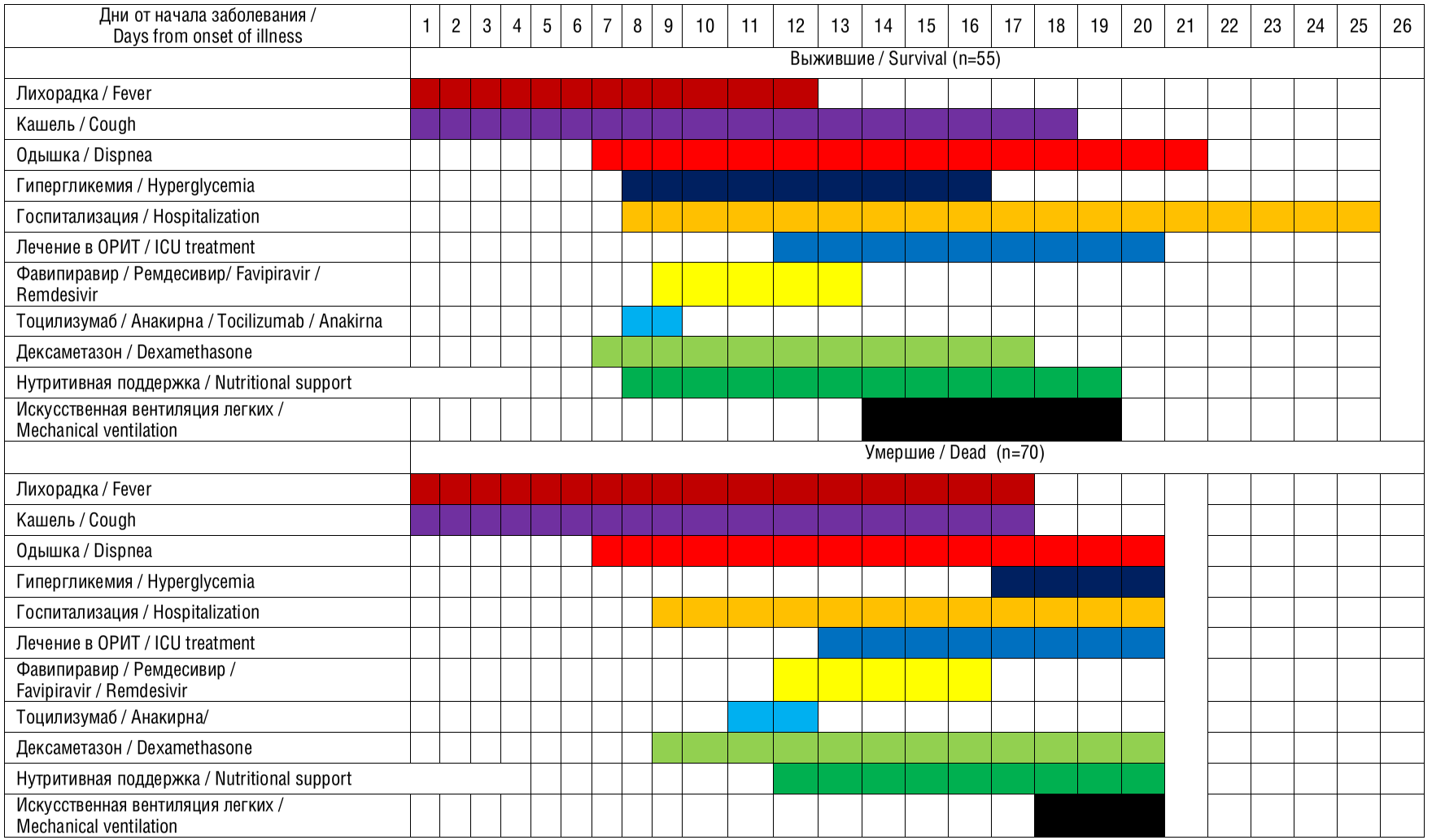

Fig. 1. Clinical course of the main symptoms and treatment tactics of stratified groups of patients with COVID-19 pneumonia and comorbid diseases. ICU — intensive care unit

Рис. 1. Клиническое течение основных симптомов и тактики лечения стратифицированных групп пациентов с COVID-19 пневмонией и коморбидными заболеваниями. ОРИТ — отделение реанимации и интенсивной терапии

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Table 3

Time trends of the vital characteristics of stratified groups of patients with COVID-19 pneumonia

Таблица 3

Временные тренды жизненно важных характеристик у стратифицированных групп пациентов с COVID-19 пневмонией

Показатели / Indicators	Выжившие / Survival (n=55)			Умершие / Dead (n=70)			p
	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	
САД, мм рт.ст. / MAP, mm Hg	95,0 (83,7–106,3)	93,8 (74,8–112,8)	87,8 (72,1–103,5)	95,1 (85,1–105,1)	96,2 (83,6–108,8)	89,6 (71,8–107,4)	Нд / Ud
ЧСС, мин / RR, min	89,7 (75,2–104,2)	86,2 (72,8–99,6)	92,6 (72,5–112,7)	87,4 (76,0–98,8)	84,4 (70,3–98,5)	85,9 (69,7–102,1)	Нд / Ud
ЧДД, мин / HR, min	23,4 (20,9–25,9)	25,2 (22,6–27,8)	28,1 (23,0–33,2)	23,3 (20,3–26,3)	23,8 (20,6–27,0)	25,4 (20,8–30,0)	Нд / Ud
Температура тела / Body temperature, °C	37,4 (36,7–38,1)	36,9 (36,3–37,5)	36,9 (36,2–37,6)	37,3 (36,6–38,0)	36,9 (36,5–37,3)	36,6 (35,9–37,3)	Нд / Ud
SpO_2/FiO_2	177,4 (164,1–190,4)	115,2 (67,6–162,8)	90,4 (76,3–104,5)	174,8 (158,4–191,2)	120,8 (58,7–182,9)	90,0 (76,7–103,3)	Нд / Ud
Гемоглобин, г/л / Hemoglobin, g/l	125,8 (100,4–151,2)	119,8 (93,7–145,9)	115,0 (89,5–140,5)	124,2 (96,8–151,2)	123,4 (99,9–157,0)	114,1 (87,9–140,3)	Нд / Ud
Эритроциты, × 10^6/мкл / Erythrocyte, ×10^6/vcl	4,2 (3,3–5,1)	3,9 (3,1–4,7)	3,9 (3,0–4,7)	4,2 (3,4–5,0)	4,1 (3,3–4,9)	3,9 (3,0–4,8)	Нд / Ud
Лейкоциты, ×10^3/мкл / Leukocyte, ×10^3/vcl	8,4 (4,2–12,6)	11,6 (5,6–17,6)	14,7 (6,1–23,3)	8,9 (3,3–14,5)	12,5 (5,1–19,9)	15,5 (4,2–26,8)	Нд / Ud
Лимфоциты, ×10^3/мкл / Lymphocyte, ×10^3/mcl	1,15 (0,35–1,95)	0,83 (0,20–1,46)	0,90 (0,15–1,65)	1,03 (0,37–1,69)	0,66 (0,06–1,24)	0,68 (0,14–1,22)	Нд / Ud
Нейтрофилы, ×10^3/мкл / Neutrophils, ×10^3/mcl	8,4 (7,4–9,3)	8,8 (7,9–9,7)	8,5 (7,3–9,7)	8,1 (6,8–9,4)	8,4 (7,5–9,4)	8,6 (7,6–9,6)	Нд / Ud
Тромбоциты, ×10^3/мкл / Platelets, ×10^3/mcl	194,1 (100,5–187,7)	216,2 (103,1–329,3)	193,6 (78,5–308,7)	202,4 (112,2–292,6)	214,7 (111,2–318,2)	206,0 (94,5–317,5)	Нд / Ud
СОЭ, мм/час / ESR, /mm/h	37,8 (21,9–53,7)	42,6 (11,4–73,8)	31,9 (9,9–53,9)	33,4 (14,2–52,6)	31,9 (15,7–48,1)	27,4 (9,3–45,5)	Нд / Ud
Глюкоза, ммоль/л / Glucose, mmol/l	9,1 (3,7–14,5)	9,3 (4,6–14,0)	10,2 (6,7–15,7)	8,4 (4,8–12,0)	8,2 (4,4–12,0)	10,2 (2,1–18,3)	Нд / Ud
Натрий, ммоль/л / Sodium, mmol/l	139,2 (131,4–147,0)	139,8 (132,4–209,6)	143,2 (132,7–153,7)	138,1 (131,7–144,5)	138,5 (133,1–143,9)	141,6 (133,5–149,7)	Нд / Ud
Калий, ммоль/л / Potassium, mmol/l	4,4 (3,3–5,5)	4,3 (3,6–5,0)	4,7 (3,4–6,0)	4,6 (3,4–5,8)	4,2 (3,3–5,1)	4,7 (3,2–6,2)	Нд / Ud
Креатинин, мкмоль/л / Creatinine, mcmol/l	107,5 (29,7–185,3)	101,1 (32,6–209,6)	118,5 (60,7–220,2)	87,9 (42,6–133,2)	82,7 (32,7–147,6)	101,0 (58,0–198,0)	Нд / Ud
Билирубин, мкмоль/л / Bilirubin, mcmol/l	8,9 (3,2–15,0)	10,6 (4,9–26,3)	12,4 (7,0–25,5)	12,5 (3,2–32,2)	10,4 (6,0–24,8)	8,6 (3,9–14,3)	0,004
АЛТ, Ед/л / ALT, un/l	35,3 (16,5–54,1)	39,0 (12,8–65,2)	42,7 (10,3–85,2)	33,4 (17,1–59,7)	39,8 (12,7–66,9)	52,9 (13,8–102,0)	Нд / Ud
АСТ, Ед/л / AST, un/l	53,6 (17,8–89,4)	54,1 (12,5–105,7)	64,1 (18,5–99,7)	54,7 (10,2–99,2)	63,9 (13,9–150,0)	62,9 (11,7–107,2)	Нд / Ud
МНО / INR	1,1 (0,9–1,3)	1,2 (1,0–1,4)	1,3 (0,9–1,7)	1,2 (0,8–1,6)	1,2 (0,9–1,5)	1,3 (0,7–1,9)	Нд / Ud

Ending of the table 3 / Окончание табл. 3

Показатели / Indicators	Выжившие / Survival (n=55)			Умершие / Dead (n=70)			p
	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	Госпитализация / Hospitalization	Перевод в ОРИТ / ICU transfer	Начало ИВЛ / Start MV	
АЧТВ, сек / APTT, sec	33,9 (25,1–42,7)	33,8 (25,3–42,3)	36,5 (19,7–53,3)	32,6 (24,1–41,1)	34,4 (18,6–50,2)	33,7 (20,2–47,2)	Нд / Ud
Фибриноген, г/л / Fibrinogen, g/l	5,2 (4,1–6,3)	4,8 (3,4–6,2)	4,1 (2,8–5,4)	4,7 (3,5–5,9)	4,7 (3,1–6,3)	3,5 (2,2–4,8)	Нд / Ud
D-димер, нг/мл / D-dimer, ng/ml	1409 (365–3154)	1506 (419–2993)	1532 (1249–2782)	2453 (773–4133)	1850 (424–3274)	3031 (1759–4303)	0,001
Белок, г/л / Protein, g/l	62,6 (50,4–74,8)	57,3 (68,4–66,2)	50,9 (43,2–58,6)	66,3 (59,0–73,6)	59,0 (50,4–67,6)	54,0 (45,3–62,7)	Нд / Ud
Альбумин, г/л / Albumen, g/l	32,5 (26,4–38,6)	28,6 (24,0–33,2)	26,2 (20,4–32,0)	32,8 (26,1–39,5)	30,5 (24,4–36,6)	29,4 (24,8–34,0)	Нд / Ud
Прокальцитонин, нг/мл / Procalcitonin, ng/ml	2,7 (0,7–8,1)	1,7 (0,9–5,5)	2,8 (0,8–8,8)	2,8 (0,8–6,7)	5,6 (2,2–17,9)	11,2 (4,5–17,9)	Нд / Ud
СРБ, мг/л / CRP, mg/l	101,7 (15,1–188,3)	98,9 (14,4–193,4)	97,3 (24,3–153,9)	123,5 (23,2–245,9)	106,9 (17,6–196,2)	118,1 (12,2–234,0)	Нд / Ud

Note: ALT — alanine aminotransferase; AST — aspartate aminotransferase; APTT — activated partial thromboplastin time; CRP — C-reactive protein; ESR — erythrocyte sedimentation rate; HR — heart rate; ICU — intensive care unit; INR — international normalized ratio; MAP — mean arterial pressure; MV — Mechanical ventilation; RR — respiratory rate; ud — unreliable differences; FiO_2 — fraction of inspired oxygen; SpO_2 — blood oxygen saturation.
Примечание: АЛТ — аланинаминотрансфераза; АСТ — аспартатаминотрансфераза; АЧТВ — активированное частичное тромбопластиновое время; ИВЛ — искусственная вентиляция легких; МНО — международное нормализованное отношение; нд — недостоверные отличия; ОРИТ — отделение реанимации и интенсивной терапии; САД — среднее артериальное давление; СОЭ — скорость оседания эритроцитов; СРБ — С-реактивный белок; ЧДД — частота дыхательных движений; ЧСС — частота сердечных сокращений; FiO_2 — фракция вдыхаемого кислорода; SpO_2 — сатурация крови кислородом.

lymphopenia without dynamics was observed in deceased patients. D-dimer levels were clearly elevated in deceased compared to surviving patients throughout the clinical course and increased as the course of the disease worsened. In deceased patients, procalcitonin levels increased rapidly from day 7–8 after disease onset, whereas CRP levels decreased from day 12 of illness in surviving patients. Daily values of three parameters (respiratory rate, erythrocyte sedimentation rate, and total bilirubin) were statistically significantly associated with a lower risk of death. The prognostic value of time trend was statistically significantly higher for two parameters (D-dimer and procalcitonin levels) compared with their daily values.

ROC-analysis of multiple clinical and laboratory parameters of heart, lung, kidney, liver and blood coagulation system at the time of hospitalization was performed. Only age >71 years, BMI >29.8 kg/m^2, D-dimer levels >1600 ng/mL and procalcitonin levels >3.4 ng/mL were strongly associated with the risk of death (Table 4). At the same time, the degree of comorbidity severity (Charlson index) almost did not determine the outcome of the disease.

Assessment of Kaplan-Meier survival curves showed statistically significantly lower survival in elderly patients with higher BMI. Moreover, they had higher levels of biomarkers (Table 5).

DISCUSSION

Clinical and laboratory parameters, as well as outcomes of consecutively hospitalized patients with comorbid diseases who had severe acute respiratory failure associated with COVID-19 pneumonia were described in the research. In order to identify risk factors for death, daily values and time trends of 23 clinical and laboratory parameters associated with acute organ dysfunction, blood coagulation disorders, and inflammatory response during the first 5 days of treatment and their relationship with mortality were analyzed. The majority of patients were hospitalized in ICU due to acute hypoxemic respiratory failure, which required respiratory support ranging from high-flow oxygen therapy to ventilator support. Overall mortality amounted to 56.0%, reaching 81.4% in patients on ALV. 34.4% of patients required ALV, which was consistent with previously published data ranging from 15 to 71%. The rate of NIVL use was 65.6% which appeared to be higher than previously cited rates varying from 14 to 62% [8, 12, 15, 18, 20].

Table 4

Operational characteristics of ROC-analysis

Таблица 4

Операционные характеристики ROC-анализа

Характеристики / Characteristics	Точка разделения / Cut of point	Площадь под ROC-кривой / AUG ROC	95% ДИ / CI	p
Возраст, лет / Age, year	71	0,69	0,61–0,78	0,001
ИМТ, кг/м^2 / BMI, kg/m^2	29,8	0,61	0,51–0,69	0,047
Индекс Чарльсона, баллы / Charleson Index, points	3	0,57	0,48–0,66	0,154
Кортикостероиды, сутки назначения / Corticosteroids, daily prescription	8	0,80	0,69–0,85	0,001
D-димер, нг/мл / D-dimer, ng/ml	1600	0,62	0,53–0,70	0,023
Прокальцитонин, нг/мл / procalcitonin, ng/ml	3,4	0,57	0,48–0,66	0,099

Note: CI — confidence interval; IBM — body mass index.
Примечание: ДИ — доверительный интервал; ИМТ — индекс массы тела.

Table 5

Comparison of Kaplan–Meier survival curves

Таблица 5

Сравнение кривых выживаемости Каплана–Мейера

Характеристики / Characteristics	OP / OR	95% ДИ / CI	Величина p / Magnitude p
Возраст >71 года / Age >71 years	2,83	1,75–4,58	0,001
ИМТ >29,8 кг/м^2 / BMI >29.8 kg/m^2	1,60	1,07–2,66	0,044
Индекс Чарльстона >3 баллов / Charleson Index >3 points	1,35	0,69–2,64	0,310
Кортикостероиды >8 суток назначения / Corticosteroids >8 days of prescription	3,67	2,24–6,00	0,001
Д-димер >1600 нг/мл / D-dimer >1600 ng/ml	2,09	1,16–3,78	0,010
Прокальцитонин >3,4 нг/мл / Procalcitonin >3.4 ng/ml	2,19	1,24–3,89	0,003

Note: CI — confidence interval; IBM — body mass index; OR — odds ratio.
Примечание: ДИ — доверительный интервал; ИМТ — индекс массы тела; ОР — отношение рисков.

Our cohort trial identified several clear adverse outcome factors in patients with COVID-19 pneumonia and comorbid conditions. Among them there were age older than 71 years, BMI greater than 29.8 kg/m^2, levels of D-dimer greater than 1600 ng/mL and procalcitonin greater than 3.4 ng/mL. These factors were associated with higher risks of in-hospital mortality. It has been previously reported that older age is an important independent predictor of mortality in SARS and MERS [4, 11]. Our findings confirm that patient mortality was particularly high among elderly males. The median age of patients hospitalized in ICU was 69.0 (59.7–79.2) years, indicating that older age is a risk factor.

Two parameters of risk factors for death showed a statistically significant greater difference in time trends between surviving and deceased patients than their daily value. Thus, it confirms the data that changes in clinical parameters during the first days of treatment differ between surviving and deceased patients and that the dynamics of variables during treatment are more relevant than their daily value at the time of patient hospitalization [13, 16, 17, 19]. A strong association between the risk of death and a biomarker of coagulation system dysfunction was found.

The influence of D-dimer time trend levels in relation to the risk of death exceeded the daily value of this parameter on any day of measurement. Many clinical and laboratory parameters of organ failure and inflammatory response, which were recorded at the time of hospitalization of patients, were greater in deceased patients, and these differences increased in the course of treatment. Thus, early and timely detection of the time trend of the most threatening parameters at the time of hospitalization may help to reduce organ damage and optimize treatment. At the same time, there was no relationship between the degree of comorbidity severity and the risk of developing lethal

outcome. There are several limitations in the study. Data on pre-existing comorbid conditions were obtained from the medical information system, hence their severity was not assessed. Considering a difficult study period, not all laboratory tests were performed in all patients, including lactate dehydrogenase and serum ferritin, so their role in predicting unfavorable outcome may be underestimated. Interpretation of results may be limited by a small sample of patients. A larger sample may help to determine prognostic values of predictors of adverse outcomes such as hospitalization in ICU, ALV or death.

CONCLUSION

1. Increased risk of death in patients with COVID-19 pneumonia and comorbid diseases was associated with older age (OR 2.83; 95% CI 1.75–4.58; p=0.001) and high BMI (OR 1.60; 95% CI 1.07–2.66; p=0.044), but not with comorbid diseases.

2. Time trends of clinical and laboratory parameters associated with acute organ dysfunction or systemic inflammation such as high levels of D-dimer (OR 2.09; 95% CI 1.16–3.78; p=0.010) and procalcitonin (OR 2.19; 95% CI 1.24–3.89; p=0.003), have greater prognostic value compared to their daily single rates.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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INVOLVEMENT OF NORADRENALINE, SEROTONIN AND BRAIN NEUROTROPHIC FACTOR IN THE ANALGETIC EFFECTS OF VASOPRESSIN IN THE THERMAL TAIL IMMERSION TEST IN RATS

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Abstract. The study of the role of the neuroendocrine system in the modulation of pain remains relevant. The analgesic properties of arginine vasopressin (AVP) are known, but the mechanisms underlying these effects are poorly understood. The aim of the study was to evaluate the effect of vasopressin receptor agonist type 2, 1-deamino-8-D-arginine-vasopressin, DDAVP, on pain sensitivity and the content of norepinephrine (NE), serotonin (5-HT), dopamine (DA) and brain neurotrophic factor (BDNF) in the parietal cortex and spinal cord in the test of thermal immersion of the tail in rats. The study was conducted on male Wistar rats. The animals were divided into 4 groups: group 1 — intact rats; group 2 — received saline solution; Group 3 — received DDAVP in a single dose of 2 ng and a cumulative dose of 10 ng; group 4 — received DDAVP in a single dose of 2 μg and a cumulative dose of 10 μg. DDAVP was administered intranasally once a day for 5 days. The saline solution was administered according to the peptide application scheme. The content of corticosterone in blood serum was determined by enzyme immunoassay. The content of NE, 5-HT, DA and their metabolites in the brain was assessed using high-performance liquid chromatography. BDNF levels were assessed using enzyme immunoassay. DDAVP in different doses reduced pain sensitivity in rats. When DDAVP was administered in small doses, the content of NE decreased in the parietal cortex; NE levels increased and 5-HT content decreased in the spinal cord. After administration of the peptide in large doses, the content of NE decreased in the parietal cortex, and the levels of 5-HT decreased in the spinal cord. DDAVP in different doses increased the content of BDNF in the parietal cortex and spinal cord. Thus, it was found that DDAVP-induced analgesia is associated with the modulatory effect of the peptide on the exchange of NE, 5-HT and BDNF at the supraspinal and spinal levels.

Keywords: vasopressin, pain, corticosterone, norepinephrine, serotonin, dopamine, brain neurotrophic factor

ВОВЛЕЧЕНИЕ НОРАДРЕНАЛИНА, СЕРОТОНИНА И НЕЙРОТРОФИЧЕСКОГО ФАКТОРА МОЗГА В АНАЛГЕТИЧЕСКИЕ ЭФФЕКТЫ ВАЗОПРЕССИНА В ТЕСТЕ ТЕПЛОВОЙ ИММЕРСИИ ХВОСТА У КРЫС

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Резюме. Сохраняет свою актуальность изучение роли нейроэндокринной системы в модуляции боли. Известны аналгетические свойства аргинин-вазопрессина (АВП), но механизмы, лежащие в основе этих эффектов, изучены мало. Целью исследования была оценка влияния агониста рецепторов вазопрессина 2-го типа, 1-дезамино-8-D-аргинин-вазопрессина (ДДАВП) на болевую чувствительность и содержание норадреналина (NE), серотонина (5-HT), дофамина (DA), нейротрофического фактора мозга (BDNF) в теменной коре и спинном мозге в тесте тепловой иммерсии хвоста у крыс. Исследование проведено на самцах крыс линии Вистар. Животных разделили на 4 группы: 1-я группа — интактные крысы; 2-я — получившие физиологический раствор; 3-я — получившие ДДАВП в однократной дозе 2 нг и кумулятивной дозе 10 нг; 4-я — получившие ДДАВП в однократной дозе 2 мкг и кумулятивной дозе 10 мкг. ДДАВП вводили интраназально 1 раз в день в течение 5 дней. Физиологический раствор вводили по схеме применения пептида. Содержание кортикостерона в сыворотке крови определяли с помощью иммуноферментного анализа. Оценивали содержание NE, 5-HT, DA и их метаболитов в мозге с использованием высокоэффективной жидкостной хроматографии; уровни BDNF — с применением иммуноферментного анализа. ДДАВП в разных дозах снижал болевую чувствительность у крыс. При введении ДДАВП в малых дозах в теменной коре снизилось содержание NE; в спинном мозге повысились уровни NE, снизилось содержание 5-HT. После введения пептида в больших дозах в теменной коре уменьшилось содержание NE, в спинном мозге — уровни 5-HT. ДДАВП в разных дозах увеличивал содержание BDNF в теменной коре и спинном мозге. Таким образом, было установлено, что вызванная ДДАВП аналгезия связана с модуляторным влиянием пептида на обмен NE, 5-HT и BDNF на супраспинальном и спинальном уровнях.

Ключевые слова: вазопрессин, боль, кортикостерон, норадреналин, серотонин, дофамин, нейротрофический фактор мозга

INTRODUCTION

Exploring mechanisms that cause pain and searching for new ways of its reduction remains actual. Recently, there has been considerable interest in analogs of endogenous neuropeptides, especially through their intranasal administration in clinical practice. One of such substances is arginine vasopressin (AVP), which exhibits peripheral and central properties [3, 4, 9]. AVP realizes its effects by activation of three types of receptors: V1aR, V1bR and V2R [9]. The involvement of V1aR in pain modulation has been established [4, 20]. The role of V2R in this process is poorly understood. The neurochemical mechanisms of the analgesic effects of AVPs are practically unknown.

It was previously shown that AVP and the V2R agonist, 1-desamino-8-D-arginine-vasopressin (DDAVP), caused analgesia in rats in models of acute and chronic pain, under different types of exposure (thermal, mechanical, chemical), and during central and peripheral administration of the peptide [4]. It is known that AVP is involved in modulating stress-responsiveness, and stress can induce analgesia [6, 17]. Clinical trials have shown that DDAVP reduced the severity of tension headaches, renal colic, and pain caused by orthopedic interventions and degenerative-dystrophic spine diseases when administered intranasally [1, 11, 24, 25].

The involvement of noradrenergic, serotoninergic and dopaminergic systems, brain-derived neurotrophic factor (BDNF) in pain modulation is well known [4, 13, 16]. According to the literature, administration of AVP and DDAVP caused changes in the levels of norepinephrine (NE), serotonin (5-NT), dopamine (DA), and BDNF in brain and blood in rats [2, 4, 30]. There are no data on the effect of DDAVP on pain sensitivity, BDNF content and monoamine neurotransmitters in the model of acute thermal pain in rats.

AIM

The aim of the research was to evaluate the effect of 1-desamino-8-D-arginine-vasopressin when administered intranasally. Pain sensitivity and brain content of norepi-

nephrine, serotonin, dopamine and their metabolites, brain neurotrophic factor were examined using the thermal tail immersion test in rats.

MATERIALS AND METHODS

30 sexually mature male Wistar rats were analyzed (Rappolovo nursery, initial body weight 220±25 g), all rats were kept under standard vivarium conditions. All animals were divided into 4 groups by the method of block randomization: Group 1 included 8 intact rats (control group, CG); Group 2 — 7 animals that received saline solution; Group 3 — 7 rats that received DDAVP in a single dose of 2 ng and cumulative dose of 10 ng; Group 4 — 8 animals that received DDAVP in a single dose of 2 μg and cumulative dose of 10 μg. Rats were injected with synthetic analog of AVP, water solution of DDAVP, Ferring s.p.a., Italy, intranasally once a day for 5 days. Saline solution was administered according to the scheme of DDAVP administration.

Thermal irritation of tail skin was performed by immersing it in a container with water heated to a temperature of 52.0±0.1 °C [5]. To determine the nociceptive response threshold (NRT), tail retraction time in seconds was recorded. Mean NRP values were determined in each animal using 6-fold measurements. The percentage of analgesia (% A) was calculated using the formula:

$$A = (P – D) / (15 – D) – 100\%,$$

where A is the percentage of analgesia or the percentage of maximum possible effect; P is the latent period of reaction in seconds after administration of DDAVP or saline solution; D is the latent period before drug administration; 15 s is the maximum time of heat exposure in seconds [20].

Following the last latency measurement, all animals were euthanized by decapitation, mixed arteriovenous blood was obtained, and the brain and spinal cord with L_5–S_2 spinal roots were extracted. After blood was collected, a tube was placed in a thermostat (37°C) and incubated for 30 min until clot formation, then the clot was gently separated from the tube walls, the sample was centrifuged for 10 min at 200 g and the supernatant (serum) was collected. Blood corticosterone content was estimated in the serum collected after euthanasia using a commercial reagent kit by Enzo № ADI-900-097 ELISA kit. All manipulations were performed in exact accordance with the instructions.

In order to determine the content of neurotransmitters and their metabolites, brain tissue samples were homogenized in 0.1 H perchloric acid, centrifuged for 30 min at 10,000 g and 4 °C, and the supernatant was collected. The levels of NE, 5-HT, DA and their metabolites (3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5HIAA)) were determined by using high-performance liquid chromatography according to the technique [31].

To determine BDNF content, brain tissue samples were homogenized with a hand homogenizer in lysis buffer (20 mM Tris, 150 mM NaCl, 0.1% Triton X-100, 5 mM EDTA, 1 mM FMSF, pH 7.6). Then the samples were centrifuged for 20 min at 4 °C, 5000 g and the supernatant was collected. The samples were stored at –70 °C. The concentration of BDNF in tissue homogenates was determined by enzyme-linked immunosorbent assay using a commercial reagent kit Rat BDNF ELISA Kit (ab213899); the procedure was performed according to the manufacturer's instructions.

Statistical analysis was performed using STATISTICA 8.0 program (StatSoft, USA). Normality of distribution was checked by the Shapiro-Wilk test. All data were expressed as mean values ± standard deviation. Statistical differences were tested using Student's criterion for independent samples or analysis of variance (for dependent or independent samples) followed by Tukey's post-hoc test. $p < 0.05$ was regarded as statistically significant.

RESULTS

There were no differences in pain sensitivity in the CG and the rest of the groups before administration of saline and

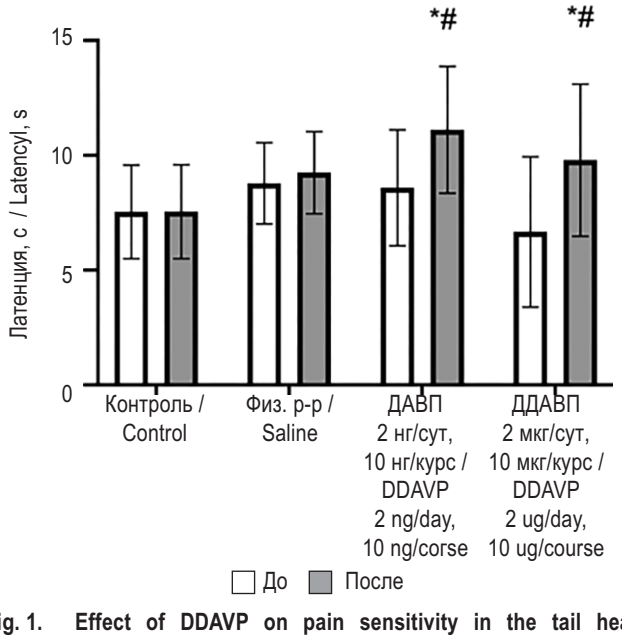

Fig. 1. Effect of DDAVP on pain sensitivity in the tail heat immersion test in rats (M±SEM, s). * — difference from control group at p <0.05; # — difference before and after administration of DDAVP at p <0.05

Рис. 1. Влияние ДДАВП на болевую чувствительность в тесте тепловой иммерсии хвоста у крыс (M±SEM, с). * — отличие от КГ при p <0,05; # — отличие до и после введения ДДАВП при p <0,05

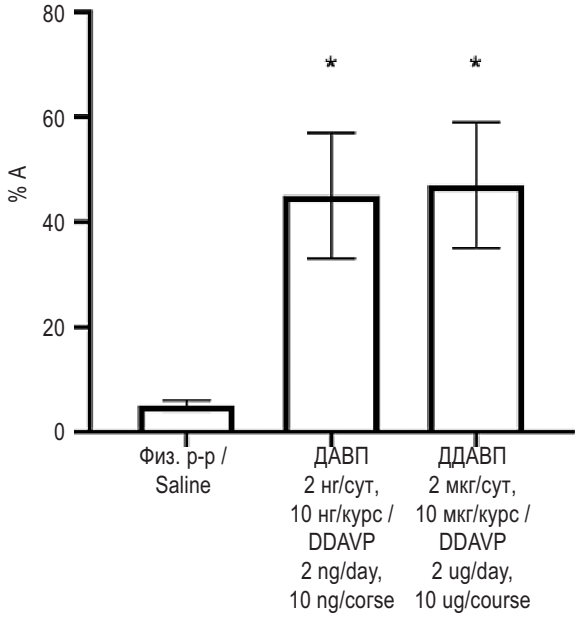

Fig. 2. Percentage of analgesia upon administration of DDAVP in the tail heat immersion test in rats. * — difference from the introduction of saline solution at p <0.05

Рис. 2. Процент аналгезии при введении ДДАВП в тесте тепловой иммерсии хвоста у крыс. * — отличие от введения физиологического раствора при p <0,05

Table 1

Serum corticosterone content in rats after administration of DDAVP (M±SEM, ng/ml) in the tail heat immersion test in rats

Таблица 1

Содержание кортикостерона в сыворотке у крыс после введения ДДАВП (M±SEM, нг/мл) в тесте тепловой иммерсии хвоста у крыс

Группы животных / Groups of animals	Содержание кортикостерона, нг/мл / Corticosterone content, ng/ml
Контрольная группа / Control group (n=8)	256±23
Физиологический раствор / Saline (n = 7)	269±23
ДДАВП (2 нг/сут, 10 нг/курс; n=7)/ DDAVP (2 ng/day, 10 ng/course; n=7)	325±40
ДДАВП (2 мкг/сут, 10 мкг/курс; n=8) / DDAVP (2 μg/day, 10 μg/course; n=8)	355±34

Table 2

Effect of DDAVP on the content of BDNF, neurotransmitters and their metabolites in the parietal cortex of rats

Таблица 2

Влияние ДДАВП на содержание BDNF, нейромедиаторов и их метаболитов в теменной коре у крыс

Показатель / Indication	Контроль / Control (n=5)	Физиологический раствор / Saline (n=7)	ДДАВП / DDAVP	
			2 нг/сут, 10 нг/курс / 2 ng/day, 10 ng/course (n=7)	2 мкг/сут, 10 мкг/курс / 2 μg/day, 10 μg/course (n=7)
BDNF, пг/мг / BDNF, pg/mg	20,6±1,62	25,60±1,69	39,80±6,58*	29,63±4,28*
NE, нг/мг белка / NE, ng/mg protein	2,42±0,64	1,80±1,18	0,32±0,20*	0,26±0,14*
DA, нг/мг белка / DA, ng/mg protein	0,29±0,20	0,30±0,17	0,74±0,23	0,46±0,21
DOPAC, нг/мг белка / DOPAC, ng/mg protein	0,33±0,17	0,30±0,18	0,32±0,13	0,47±0,14
HVA, нг/мг белка / HVA, ng/mg protein	0,26±0,16	0,16±0,09	0,23±0,13	0,26±0,10
5-HT, нг/мг белка / HVA, ng/mg protein	0,27±0,18	1,78±1,10	1,43±0,54	1,36±1,12
5-HIAA, нг/мг белка / 5-HIAA, ng/mg protein	2,98±1,26	3,91±1,52	1,78±0,51	3,19±0,81

Note: * — differences compared to control group at p <0.05
Примечание: * — отличия по сравнению с контрольной группой при p <0,05.

Table 3

Effect of DDAVP on the content of BDNF, neurotransmitters and their metabolites in the spinal cord of rats (M±SEM, units)

Таблица 3

Влияние ДДАВП на содержание BDNF, нейромедиаторов и их метаболитов в спинном мозге у крыс (M±SEM, единицы)

Показатель / Indication	Контроль / Control (n=5)	Физиологический раствор / Saline (n=7)	ДДАВП / DDAVP	
			2 нг/сут, 10 мкг/курс / 2 ng/day, 10 μg/course (n=7)	2 мкг/сут, 10 мкг/курс / 2 μg/day, 10 μg/course (n=7)
BDNF, пг/мг / BDNF, pg/mg	17,7±1,6	25,8±1,36	29,0±1,87*	40,6±3,3*#&
NE, нг/мг белка / NE, ng/mg protein	0,68±0,07	0,9±0,56	1,60±0,28*	0,43±0,12
DA, нг/мг белка / DA, ng/mg protein	0,46±0,1	0,67±0,19	0,64±0,13	0,57±0,09
DOPAC, нг/мг белка / DOPAC, ng/mg protein	0,32±0,10	0,56±0,05	0,50±0,11	0,43±0,16
HVA, нг/мг белка / HVA, ng/mg protein	0,10±0,07	0,05±0,05	0,13±0,05	0,09±0,04
5-HT, нг/мг белка / HVA, ng/mg protein	5,07±1,53	4,35±0,59	2,86±0,56#	1,97±0,46*
5-HIAA, нг/мг белка / 5-HIAA, ng/mg protein	1,57±0,64	1,25±0,34	0,66±0,12	1,19±0,23

Note: * — differences compared to the control group at p <0.05; # — difference compared to the introduction of saline at p <0.05; & — differences when administering small and large doses of the peptide.
Примечание: * — отличия по сравнению с контрольной группой при p <0,05; # — отличие по сравнению с введением физиологического раствора при p <0,05; & — отличия при введении малых и больших доз пептида.

DDAVP at different doses (Fig. 1). DDAVP at low and high doses increased PNR in rats (Tukey's criterion, p=0.00001, p=0.00001, respectively) (Fig. 1). PNRs were higher after administration of low- and high-dose DDAVP compared with CG (F(3,26)=12.95, p=0.00002; Tukey's criterion, p=0.01, p=0.04, respectively).

When DDAVP was administered, % A amounted to 45.3±12.0% at low doses and 45.5±11.4% at high doses, which was higher compared to saline administration (F(2,19)=4.6, p=0.023, Tukey's criterion, p=0.04, p=0.03, respectively) (Figure 2), it did not affect serum corticosterone content in different doses (Table 1).

After low-dose DDAVP administration, NE levels decreased in parietal cortex compared to CG (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04); BDNF levels increased (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04) (Table 2). Low-dose DDAVP in the spinal cord decreased 5-NT levels (F(3,21)=3.58; p=0.03); increased BDNF levels (F(3,16)=28.47, p=0.0001; Tukey's criterion, p=0.01) (Table 3).

After high-dose DDAVP administration, NE levels decreased in parietal cortex compared to CG (F(3,21)=3.78; p=0.02; Tukey's criterion, p=0.04); BDNF levels increased (F(3,16)=3.89; p=0.029; Tukey's criterion, p=0.04) (Table 2). High-dose DDAVP in the spinal cord decreased 5-NT levels (F(3,21)=3.45; p=0.03); increased BDNF levels compared to CG, saline and low-dose peptide administration compared to CG (F(3,19)=14.78, p=0.00003; Tukey's criterion, p=0.0001; p=0.0002; p=0.0004, respectively) (Table 3).

Thus, DDAVP reduced pain sensitivity in the thermal tail immersion test in rats, when administered intranasally at different doses. Analgesia was associated with similar changes in NE, 5-NT and BDNF content in the brain regardless of administered doses of DDAVP. Low-dose dDAVP decreased NE content in parietal cortex, increased NE levels, and decreased 5-NT content in the spinal cord. DDAVP at high doses decreased NE content in parietal cortex and decreased 5-NT levels in the spinal cord. DDAVP at different doses increased BDNF content in cortex and spinal cord.

DISCUSSION

This work revealed an analgesic effect of V2R agonist, DDAVP, when administered intranasally in the tail heat immersion test in rats for the first time. The obtained results are comparable to the data acquired with intraventricular administration of AVP [14].

To date, the exact mechanisms of peptide penetration into the brain during intranasal administration remain poorly understood. At the same time, it is believed that under these conditions the central and peripheral effects of AVPs are due to both its direct penetration into the central nervous system and its non-direct penetration through the systemic

bloodstream [28]. The research showed that different doses of DDAVP did not affect the content of corticosterone in blood, hence, did not cause stress-induced analgesia.

It is known that AVP induces analgesia by activating mainly its own receptors. According to the literature, AVP-induced analgesia at the supraspinal level is caused by activation of V1aR and V2R in the brain nuclei [26, 27, 29]; whereas the spinal cord and spinal ganglia are affected by V1aR [19].

Впервые показано участие норадренергической и серотDDAVP was proved to exercise analgesic effects on noradrenergic and serotoninergic systems, as well as BDNF for the first time. It is known that the tail thermal immersion test is accomplished at the spinal level through supraspinal influences [15]. Analgesia induced by administration of DDAVP at different doses was induced by changes in NE content at supraspinal and spinal levels, 5-HT — at the spinal level. It is known that conductors containing NE and 5-HT at the supraspinal level constitute the descending antinociceptive system [7, 10, 12, 18]. At the spinal level, NE-induced analgesia is caused by activation of α2-adrenoreceptors; 5-HT-related analgesia is caused by 5-NT1A and 5-HT3 receptors [7, 17, 18].

BDNF content in parietal cortex and spinal cord increased after peptide administration at different doses. According to the literature, BDNF-induced analgesia at the supraspinal level is associated with increased activity of the serotoninergic system and release of endogenous opioid peptides [21–23]. At the spinal level, it is associated with increased GABA- and glycinergic transmission in neurons of the posterior horns of the spinal cord [8]. There is reason to believe that the identified analgesic effects of DDAVP associated with NE, 5-HT and BDNF could be caused by different molecular mechanisms at different levels of the nervous system.

CONCLUSION

1. The V2R agonist, 1-desamino-8-D-arginine-vasopressin, DDAVP, reduced pain sensitivity in rats in the tail thermal immersion test when administered intranasally at different doses.

2. Analgesia induced by DDAVP at different doses was associated with the involvement of noradrenergic system and BDNF at supraspinal and spinal levels, as well as with the involvement of serotoninergic system at the spinal cord level.

ADDITIONAL INFORMATION

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

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

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All procedures complied with ethical standards approved by legal acts of the Russian Federation, international regulations (Directive 2010/63/EU of the European Parliament and the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes), and the recommendations of the Bioethics Committee of FSBSI "IEM" (protocol No. 6/20 of October 21, 2020).

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COMPARISON OF CLINICAL OUTCOME OF BYPASS SURGERY VERSUS BELOW-THE-KNEE ANGIOPLASTY AND STENTING IN INFRAPOPLITEAL LESIONS THAT RESULTS IN ULCER OR TOE GANGRENE

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Abstract. ***Introduction.*** Chronic limb-threatening Ischaemia (CLTI) is a manifestation of peripheral arterial disease (PAD) that includes chronic ischemic rest pain or Ischaemic skin lesions, ulcers, or gangrene for longer than two weeks. Although infrapopliteal angioplasty may salvage the majority of limbs under threat of amputation. Endovascular interventions in the infrapopliteal vasculature may improve symptoms in patients with CLTI by re-establishing in-line blood flow to the foot. The optimal revascularization strategy for patients with severe leg ischemia remains uncertain. ***The purpose*** of this study was to compare outcomes of bypass surgery and angioplasty in isolated below-the-knee lesions. ***Materails and methods.*** Patients with ulcers or toe gangrenes, undergone below-the-knee bypass surgery or angioplasty and stenting from 2022 to 2023, were included in the study. Amputation-free survival (AFS) and overall survival (OS) were assessed using the Kaplan–Meier and Cox regression tests. ***Results.*** Three hundred ten (310) patients were included in this study, of which 259 patients underwent balloon angioplasty and popliteal artery stenting, 51 patients underwent bypass surgery. The mean age in the bypass group was 73.1 (±7.1) years and 73.9 (±7.2) years in the angioplasty and stenting group. There were no significant differences in gender, diabetes, hypertension, history of smoking, history of stroke, and renal insufficiency between the three groups. AFS was 43.4 (±8.5) months in the bypass group and 39.8 (±8.9) months in the angioplasty and stenting group which was significantly better in the bypass group (p=0.05). OS was 49.6 (±10.6) months in the bypass group and 46.2 (±11.7) months in the angioplasty and stenting group but did not differ statistically significant (p=0.32). ***Conclusion.*** AFS was significantly higher in the bypass group. Thus, bypass surgery seems preferable to angioplasty for all patients with severe leg ischemia except those with multiple comorbidities and those whose vein is not adequate for bypass.

Keywords: below-the-knee angioplasty, below-the-knee bypass, lower limb ischemia, toe gangrene

СРАВНЕНИЕ КЛИНИЧЕСКИХ РЕЗУЛЬТАТОВ ШУНТИРОВАНИЯ ПО СРАВНЕНИЮ С АНГИОПЛАСТИКОЙ И СТЕНТИРОВАНИЕМ НИЖЕ КОЛЕНА ПРИ ПОРАЖЕНИИ ИНФРАПОПЛИТЕАЛЬНОЙ АРТЕРИИ, ПРИВОДЯЩЕМ К ЯЗВЕ ИЛИ ГАНГРЕНЕ СТОПЫ

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Резюме. ***Введение.*** Хроническая ишемия, угрожающая потерей конечностей (ХИУПК), представляет собой конечную стадию заболевания периферических артерий (ЗПА), которое включает хроническую ишемическую боль в покое или ишемические поражения кожи, язвы или гангрену продолжительностью более двух недель. Хотя инфрапоплетиальная ангиопластика может спасти большинство конечностей при угрозе ампутации, эндоваскулярные вмешательства на инфрапоплитеальном сосудистом русле могут улучшить симптомы у пациентов с ХИУПК за счет восстановления магистрального кровотока в стопе. Оптимальная стратегия реваскуляризации у пациентов с тяжелой ишемией ног остается неопределенной. ***Целью*** данного исследования было сравнение результатов шунтирования и ангиопластики при изолированных поражениях ниже колена. ***Материалы и методы.*** В исследование были включены пациенты с язвами или гангреной пальцев ног, перенесшие операцию шунтирования ниже колена или ангиопластику и стентирование в 2022–2023 гг. Выживаемость без ампутаций (ВБА) и общая выживаемость (ОВ) оценивались с использованием регрессионных тестов Каплана–Мейера и Кокса. ***Результаты.*** В исследование были включены 310 пациентов, из них 259 пациентам была выполнена баллонная ангиопластика и стентирование подколенной артерии (ПкА), 51 пациенту — шунтирование. Средний возраст в группе шунтирования составил 73,1 (±7,1) года, а в группе ангиопластики и стентирования — 73,9 (±7,2) года. Между двумя группами не было существенных различий по полу, диабету, гипертензии, курению, инсульту и почечной недостаточности в анамнезе. ВБА составила 43,4 (±8,5) месяца в группе шунтирования и 39,8 (±8,9) месяца в группе ангиопластики и стентирования, что было достоверно лучше в группе шунтирования (p=0,05). Общая выживаемость (ОВ) составила 49,6 (±10,6) месяца в группе шунтирования и 46,2 (±11,7) месяца в группе ангиопластики и стентирования, но статистически значимо не отличалась (p=0,32). ***Заключение.*** ВБА была значительно выше в группе шунтирования. Таким образом, операция шунтирования представляется предпочтительнее ангиопластики для всех пациентов с тяжелой ишемией ног, за исключением пациентов с множественными сопутствующими заболеваниями и тех, чья вена не подходит для шунтирования.

Ключевые слова: ангиопластика ниже колена, шунтирование ниже колена, ишемия нижних конечностей, гангрена пальца стопы

INTRODUCTION

Atherosclerosis is the most common cause of peripheral arterial disease (PAD) of the lower extremities. Acute ischemic limb is an advanced stage of peripheral vascular disease, which is characterized by pain during rest and night pain (requiring opioid analgesics), for >2 weeks. This condition results in ulcers and gangrene in the limbs, and if left untreated, it will cause permanent disability, even amputation, and mortality in patients. It also imposes a heavy burden on the society and health system [1]. This condition is now cured using various revascularization technics [2]. Although surgical bypass is regarded as the gold standard due to better anatomical and clinical durability relative to the other revascularization methods for critical lower limb ischemia (CLI) [14–16], percutaneous transluminal angioplasty (PTA) in peripheral vascular disease (PVD) is a feasible method of treating CLI, and has similar outcomes to those of bypass surgery [17, 18, 23–30] (Fig. 2).

Several studies have been published about the outcomes of surgical and endovascular interventions all around the world, presenting various views on these two approa-

ches. Although both surgery and angioplasty methods are suggested for these patients, there are still significant controversies regarding the best one [1, 3–9].

Infrapopliteal bypass is one of the major methods in lower limbs, which targets to reestablish blood flow to the tibial, peroneal, or pedal arteries. The primary indication for this method is critical limb ischemia (CLI) due to atherosclerotic events [3]. In general, venous grafts, regardless of the target site, are preferred over artificial grafts in all below-the-knee bypasses. The large saphenous vein is most commonly used; however, small saphenous vein, superficial femoral vein, and venous parts of the upper limbs can also be used [4, 8, 23–30].

Endovascular treatment is often the first choice in the treatment of peripheral vascular diseases of the lower extremities [2]. New advances in endovascular treatments have made it possible to treat complicated vascular lesions. Patients with multiple underlying illnesses or those who do not have proper veins for the surgery will benefit most from endovascular therapies [2, 6].

Despite extensive studies for determining the best way to treat these patients, there is no consensus on which surgical or angioplasty is preferred (Fig. 3).

THE AIM OF THE STUDY

This study aimed to compare the results of bypass and angioplasty in patients with lesions below the knee due to ischemia, to determine which method gives better outcomes.

MATERIALS AND METHODS

In this retrospective cohort study, 310 patients who were treated by bypass surgery or angioplasty or stenting from 2022 to 2023 were included in the study. The criteria for entering the study were having obstruction or stenosis of distal to popliteal artery confirmed by duplex or triplex ultrasonography and computed tomography angiography. The exclusion criteria of patients were being unable to walk due to advanced underlying disease or due to severe deformities in the knee or ankle joints.

The patients were interviewed and examined to collect their demographic, pre and post-medical history information, including gender, age, smoking status, background illnesses, having ulcers, gangrene, or pain during rest, level of amputation, glycated hemoglobin level, and type of their surgeries (Fig. 1). Confidence interval in this study was 95%.

RESULTS

A total number of 310 patients who were undergone below-the-knee bypass surgery or angioplasty or stenting of PopA during the years of 2022–2023 because of foot ulcers or gangrene were enrolled in this study. The mean age in

Possibility of PAD
Medical history, Risk factors of atherosclerosis,
Arterial pulse palpitation, Vascular bruit, ABI

↓

Foot evaluation (WIfi classification) *Toe pressure, SSP,TcPO2, CRP, WBC, Bacterial culture*

I grade	*W grade*	*Fi grade*
Grade 3 with rest pain	*W3*	*Fi2,3*
Grade 2 with tissue loss	*Deep infection evaluation*	*Deep infection evaluation*

Diagnosis as CLI

↓

Systemic evaluation	**Vascular evaluation**	**Differential diagnosis of disease etiology**
Cardiac function, coronary circulation	Anatomy of arterial lesions	Buerger's disease
Cerebral and neck arteries	Hemodynamics (duplex)	Other vasculitis
Lung, kidney, liver function	Vein material evaluation	Collagen disease
Coagulation and fibrinolysis system	Limb function evaluation	Rare diseases involving popliteal artery
Status of lifestyle disease management	Daily activity	Other vascular disease

Fig. 1. Diagnostic steps for patients with rest pain or chronic wounds of foot: PAD — peripheral arterial disease; CLI — critical limb ischemia

Рис. 1. Диагностические этапы для пациентов с болью в покое или хроническими ранами стопы

Table 1

Demographic and descriptive statistics about age, amputation-free survival, and overall survival of patients groups

Таблица 1

Демографическая и описательная статистика о возрасте, без ампутационной выживаемости и общей выживаемости групп пациентов

Variable	Groups	N	Mean	SD	SEM
Age	Angioplasty+stenting	259	73.95	7.22	1.07
	Bypass	51	73.11	7.10	1.08
AFS	Angioplasty+stenting	259	39.82	8.98	1.33
	Bypass	51	43.44	8.57	1.30
OS	Angioplasty+stenting	259	46.28	11.76	1.75
	Bypass	51	49.67	10.68	1.62

Note: AFS — amputation-free survival; OS — overall survival: SD — standard deviation: SEM — standard error of mean.

Table 2

Таблица 2

Классификация А.В. Покровского

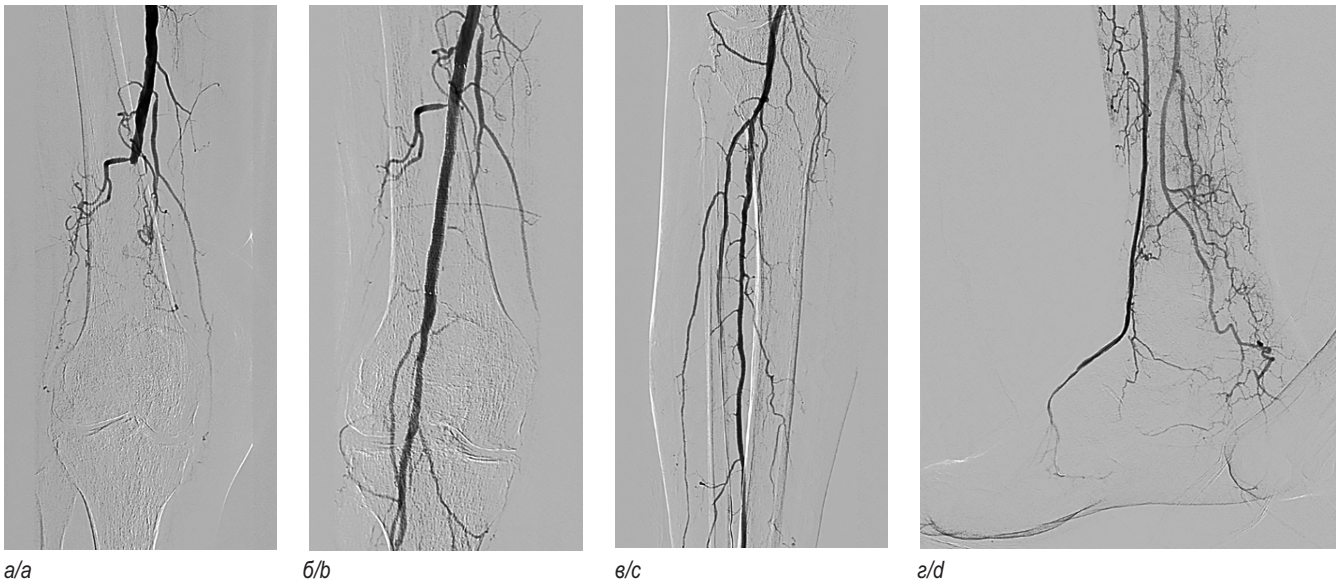
A.V. Pokrovsky classification

Stage	Symptoms
I	Asymptomatic or pain in calf muscles (>1 km)
IIA	Intermittent claudication (>200 meters)
IIB	Intermittent claudication (<200 meters)
III	Intermittent claudication, rest pain
IV	Ulceration or gangrene

the bypass group was 73.1 (±7.1) years, and in the angioplasty group was 73.9 (±7.2) years. Amputation-free survival (AFS) in the bypass group was 43.5 (±8.5) months and 39.8 (±8.9) months in the angioplasty group. AFS was significantly higher in the bypass group compared to the angioplasty group (p=0.05) (Table 1). In addition, the AFS survival survey showed that in the bypass group, the predicted survival rate was 45.1±4.29 (42.87–47.95) months, and in the angioplasty group was 41.1±7.27 (39.24–44.25) months, which showed a significant difference between the two groups (p=0.05). Patients' overall survival (OS) was 49.6±10.6 and 46.2±11.7 months in the bypass and angioplasty groups, respectively. There was no significant difference between the groups (p=0.32) (Table 1). The OS survey of patients indicated that the average predicted survival in the bypass group was 54.1±6.7 months (51.13–58.09) and in the angioplasty group was 52.2±2 months (48.3–56.1). Despite >4 months difference, it was not statistically significant (p=0.3).

DISCUSSION

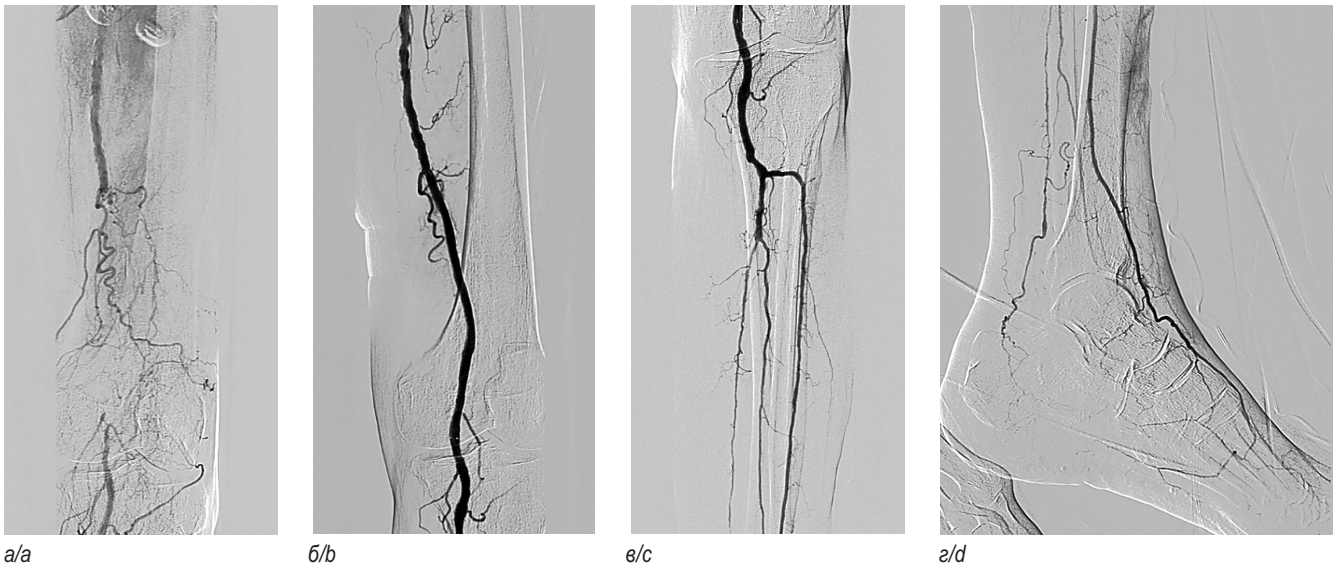
Choosing the best type of treatment for patients with lower limb ischemia is still a question. According to the Bypass versus Angioplasty in Severe Ischemia of the Leg's (BASIL's) randomized controlled trial (RCT), there was no significant difference between the results of surgical bypass and angioplasty up to 2 years. However, patients who lived >2 years benefited from bypass surgery. To the best of our knowledge, BASIL's RCT is the only one that its results are available in this regard [1]. Although BASIL 2, and BEST-CLI studies are in progress, their results have not been released yet. Therefore, considering that there is still no certainty about treatment selection, the current study aimed to collect, analyze, and report the results of both bypass and angioplasty patients with lower limb ischemia. The main goal was to answer the question of which method is better for below-the-knee lesions. Although the definition of "better" is not easy, we chose AFS as the main criterion, which is also the US Food and Drug Administration's criterion for such studies. The reason for not considering other criteria such as vascular patency and arterial pressure in the ankle (ankle pressure) was that we wanted to compare two therapeutic strategies, not just comparing bypass and angioplasty techniques. Morbidity was not evaluated in this study due to the controvert results reported in various studies pertaining to morbidity. For example, an article published by Siracuse et al.



а/a *б/b* *в/c* *г/d*

Fig. 2. Occlusion of the PopA, crural arteries on the right: *a* —initial angiogram; *b–d* — after transluminal balloon angioplasty with stenting of the PopA and lower leg arteries

Рис. 2. Окклюзия подколенной артерии (ПкА), артерий голени справа: *а* — исходная ангиограмма; *б–г* — после транслюминальной баллонной ангиопластики со стентированием ПкА и артерий голени



а/a *б/b* *в/c* *г/d*

Fig. 3. Occlusion of the PopA, crural arteries on the left: *a* — initial angiogram; *b–d* — after transluminal balloon angioplasty with stenting of the PopA and lower leg arteries

Рис. 3. Окклюзия подколенной артерии (ПкА), артерий голени слева: *а* — исходная ангиограмма; *б–г* — после транслюминальной баллонной ангиопластики со стентированием ПкА и артерий голени

indicated endovascular procedures had been associated with lower 30-day mortality rate and 3-year worse survival compared to surgical bypass [10]. In another study by Tsai et al., no significant difference was reported between these two methods regarding the 30-day mortality [11]. Moreover, studies often suggest that mortality and morbidity of the endovascular method are reduced within short-term periods. Thus, they are less indicative to determine the effectiveness of these methods, especially in long-term periods [12, 13].

The examinations showed that all of the patients, who participated in this study, had normal aortic, iliac, and femoral vessels or had no significant lesions. To the best of our knowledge, most of the previous studies analyzed the lesions under the groin area, while the current study for the first time compared these two methods in lesions below the knee. AFS in the bypass group was 43.5±8.5 and in the angioplasty group, it was 39.8±8.9 months, which showed a significant difference with p=0.05

(Table 1). In addition, OS in bypass patients was 49.6±10.6 months and 46.2±11.7 months in the angioplasty patients. There was no significant difference between the two groups regarding OS (p=0.32). Regarding the fact that the mean and frequency of demographic variables such as age and gender in the two groups did not differ significantly. Thus, it cannot be hypothesized that the patients in the bypass group had better physical status. Indeed, the effects of the demographic factors were minimized. Due to the increasing prevalence of diabetes, high blood pressure, and tobacco consumption, limb ischemia appears to be one of the major problems in health systems, both in developed and developing countries.

Currently, most studies emphasizing vascular reconstruction for patients with severe lower limb ischemia are reporting very good results. However, a significant percentage of these patients undergo medical treatments. Although AFS was a clear and relevant measure in this study, it did not provide much information about the quality of life of patients after vascular reconstruction. It is quite acceptable that sometimes amputation in the early phase of the disease improves the patient's quality of life, but on the other hand, chronic pain, and wound care reduce the quality of life of the patients. As a result, this issue should be taken into attention by vascular surgeons and intervention specialists, to not only consider vascular lesions in the treatment of these patients but also patients' needs and expectations.

Although bypass surgery using outflow vessels below the ankle should be considered the standard treatment in patients with CLI due to infrapopliteal arterial disease [20], this requires a good vein conduit and at least one open foot artery and is associated with considerable perioperative mortality, postoperative complications, myocardial infarction, and early reoperation for graft thrombosis [21]. Recanalization temporarily increases blood flow to the foot and has a positive effect in eradicating infection and healing ulcers and surgical wounds. Because foot tissue healing reduces oxygen demand, less blood flow is generally required to maintain tissue integrity and keep the limb asymptomatic [19, 22].

CONCLUSION

The main finding of this study was that the surgical bypass procedure had a significantly higher AFS compared to angioplasty in the two examined groups during the follow-up period. Therefore, it is recommended for all patients with below-the-knee ischemic lesions to have surgical bypass procedures, except for patients with multiple underlying diseases, who have a high-risk condition for surgery, as well as for patients with veins not suitable for bypass.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

ADDITIONAL INFORMATION

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

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DISRUPTED SYNTHESIS OF NEUROTRANSMITTERS IN THE PATHOPHYSIOLOGY OF DIABETIC ENCEPHALOPATHY (LITERATURE REVIEW)

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Abstract. This review provides a summary of data on the role of neurotransmitter synthesis abnormalities in the pathophysiology of diabetic encephalopathy (DE). It covers the key neurotransmitters that could be involved in the pathogenesis of DE: gamma-aminobutyric acid, glutamate, dopamine, acetylcholine and serotonin. The article describes the main pathophysiological mechanisms that may play a role in the development and progression of DE in the course of diabetes mellitus in a patient with disrupted release of key neurotransmitters. It provides data confirming the hyperreactivity of the GABAergic, glutamatergic and dopaminergic systems, along with the hypoactivity of the cholinergic and serotoninergic systems, as part of the pathophysiology of DE. Also provided are results of preclinical and clinical studies confirming that patients with type 1 and 2 DM have abnormalities in the synthesis of neurotransmitters, which could serve as early diagnostic markers of DE.

Keywords: diabetic encephalopathy, gamma-aminobutyric acid, glutamate, dopamine, acetylcholine, serotonin

НАРУШЕНИЕ ВЫРАБОТКИ НЕЙРОМЕДИАТОРОВ В ПАТОФИЗИОЛОГИИ ДИАБЕТИЧЕСКОЙ ЭНЦЕФАЛОПАТИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. В обзоре обобщены данные о нарушениях выработки нейромедиаторов в патофизиологии диабетической энцефалопатии (ДЭ). Рассмотрены основные нейромедиаторы, которые могут быть задействованы в патогенезе ДЭ: гамма-оксимасляная кислота, глутамат, дофамин, ацетилхолин, серотонин. Представлены основные патофизиологические механизмы, которые могут быть задействованы в формировании и прогрессировании ДЭ по ходу течения сахарного диабета (СД) при нарушении в выработке основных нейромедиаторов. Обоснована гиперреактивность ГАМК-эргической, глутаматергической (далее — глютамат) и дофаминергической систем, а также гипоактивность холинергической и серотонинергической систем

в патофизиологии ДЭ. Приведены данные доклинических и клинических исследований, доказывающие нарушение выработки нейромедиаторов при СД 1-го и 2-го типов, которые могут служить ранними маркерами в диагностике ДЭ.

Ключевые слова: диабетическая энцефалопатия, гамма-оксимасляная кислота, глутамат, дофамин, ацетилхолин, серотонин

INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine disease characterized by elevated glucose levels and insufficient insulin production or activity [1]. This endocrinopathy is associated with well-described and studied macrovascular and microvascular complications including diabetic retinopathy, nephropathy, cardiomyopathy and peripheral neuropathy [14]. Current scientific evidence suggests that DM can also have a negative impact on the central nervous system (CNS), causing a number of neurochemical, neurophysiological and structural disorders. Collectively, these disorders contribute to the formation of a specific complication and clinical symptom complex known as diabetic encephalopathy (DE) [2, 3, 12, 41]. In this regard, studying DE is an urgent area of modern endocrinology [1, 46]. It is well known that DE can manifest as cognitive dysfunction, amnestic disorders, decreased learning ability and speed of information processing in clinical practice [1, 41, 46]. However, pathogenesis of this complication in DM remains incompletely understood [46]. At present, there are a few contestants considered as possible triggers for DE development: decreased insulin secretion or activity, impaired regulation of glucose homeostasis, increased glucocorticoid levels, development of neuroinflammation, impaired neurotransmission, oxidative stress (OS), and mitochondrial dysfunction [29, 41].

At the same time, there is a concern that preventive measures and therapies for DE should be initiated as soon as possible in order to be most effective [46]. Until now, most cognitive disorders in DM have been clinically diagnosed by physical and neurological examinations using standard neuropsychological and cognitive tests [4]. However, it is known that DE progresses rather slowly over the course of DM, over several years, before the first obvious clinical symptoms appear [35]. Thus, early diagnosis of DE remains a major challenge during the long period of progression [46].

Evidence suggests that disorders in a neurotransmitter system may be the most early pathophysiological signs of cognitive dysfunction in DM, and several neurotransmitter systems can be used as early diagnostic markers of DE [23, 32]. It is believed that neurotransmission abnormalities on the background of DM occur much earlier than structural and functional changes in the brain on the background of DM [34]. However, there is still insufficient information on neurotransmitter disorders and their pathophysiologic role in the progression of DE [46]. Therefore, the aim of this review was to highlight possible mechanisms of impaired production of key neurotransmitters and to describe their possible use as early markers of DE. Due to the limited scope of this review, only key neurotransmitters that may play a key role in the pathophysiology of DE are considered: gamma-oxybutyric acid (GABA); glutamate (GT), dopamine (DA), acetylcholine (ACh), and serotonin (ST).

GABA

The GABAergic system is a major inhibitory neurotransmitter in the brain [40]. Numerous studies support the concept of cognitive function inhibition due to the activated GABAergic system [40]. Physiologic function of the GABAergic system is impaired in DM, and dysfunction of this system may be involved in the pathophysiology of DE [33, 45]. Dysfunction of the GABAergic system plays an important role in diabetic cognitive failure and CNS damage, impaired brain energy homeostasis, and enhanced oxidative stress [45]. An imbalance between excitation and inhibition due to dysfunction of GABAergic neurons has been shown to dramatically increase glucose toxicity in the brain [41]. Preclinical studies showed that GABA levels were significantly elevated in the hippocampus of rats with type 2 DM [16]. Elevated GABA levels have been reported in plasma from patients with type 2 DM, which correlated with the level of hyperglycemia and cognitive impairment [25]. Another study showed that patients with type 2 DM had marked insulin resistance and cognitive dysfunction, as well as increased concentration of GABA in the medial prefrontal cortex [37]. Van Bassel et al. showed that patients with type 2 DM exhibit higher concentrations of GABA in the occipital lobe of the brain, which was associated with poorer cognitive abilities [39]. It is no coincidence that drugs that modulate the GABAergic system have a positive effect on memory and cognitive abilities [9]. For example, GABA antagonists and some steroids that inhibit GABA, such as pregnenolone sulfate, show significant improvement in learning and memory [1]. Thus, it can be concluded that DE is characterized by hyperactivation of the GABAergic system, and high GABA levels may serve as early biomarkers of this complication.

GLUTAMATE

GT is one of the most important excitatory neurotransmitters in the brain [19]. Namely, low concentration of GT in neurons is necessary for optimal and physiological neuronal function [10]. Although GT is an important neurotransmitter, its pathologic accumulation causes this amino acid to become a potent neurotoxin [8]. This is mainly due to the activation of glutamatergic receptors, which leads to increased calcium entry into neurons and the formation of exitotoxicity processes [8, 27, 38]. In turn, excitotoxicity leads to degeneration and death of brain neurons [21, 30].

The excitotoxic cascade in DE begins with a marked disruption of oxidative metabolism, which leads to ischemia and depolarization of brain neurons [6]. This process disables neurotransmitter reuptake pumps, including GT, resulting in the activation of anaerobic metabolism processes in the brain [6]. As a result, GT begins to work extrasynaptically, stimulating opening of glutamatergic receptor channels, which leads to an excessive intake of sodium and calcium into brain neurons [6]. Against the background of high calcium concentration in neurons, endoplasmic reticulum is stressed. Mitochondrial dysfunction and OS activation occur, which are considered to be the leading pathophysiological mechanisms of DE formation on the background of excitotoxicity and excessive GT [31].

In addition, it has been shown that excitotoxic production of reactive oxygen species increases the activity of protein kinase C, which may contribute to the death of neurons on the background of DE [31]. Regarding clinical studies, the levels of GT in the brain were higher in patients with type 1 DM compared to controls, which suggests a potential role of GT as an early marker of cerebral complications caused by hyperglycemia in type 1 DM [43]. Consequently, activation of the glutamatergic system will occur in DE, and elevated GT levels may be considered as markers of cognitive impairment.

DOPHAMINE

DA is an important neurotransmitter of the CNS. It performs a number of important physiologic functions primarily related to cerebral activity (emotion processing, cognition formation, motor activity, and cognitive abilities) [36]. Alterations in dopaminergic signaling involve neurodegenerative diseases and encephalopathy of various genesis [5, 22]. Increased DA levels constitute a major factor in developing diabetic complications in type 2 DM. One of the most dangerous complications in DM is CNS damage, and the involvement of dopaminergic system dysfunction is no longer in doubt [26]. Insulin resistance in the brain may lead to changes in mitochondrial function, increased monoamine oxidase levels and increased DA clearance [18]. Thus, DA may represent a potential biomarker of cerebral insufficiency in DM on the background of dopaminergic system hyperactivation [13].

ACETYLCHOLINE

The cholinergic system is an important modulating neurotransmitter involved in cognitive processes. ACh itself plays a leading role in learning and memory [15, 28]. It was shown that synthesis and release of ACh were significantly reduced against the background of DM decompensation [42]. Decreased level of nicotinic acetylcholine receptors and increased apoptosis in the hippocampus was found in patients with type 2 DM [44]. It has also been reported that dysfunction of the cholinergic system is directly related to altered activity of crucial brain enzymes such as acetylcholinesterase (AChE), which may be one of the reasons for cognitive deficits in animals with DE [20, 24]. Notably, the same trend was observed in the serum of animals with DE, hence serum AChE can be used as an important biomarker to detect DE in the initial stages of DM [46].

SEROTONIN

In recent years, ST levels have been considered as powerful biomarkers of DM, including DE [17]. It has been shown that blood levels of ST were lower in patients with DM compared to controls [17]. Preclinical studies demonstrated that intranasal administration of ST reduces body weight in rats with DM and improves glucose tolerance and lipid metabolism [11]. In addition, ST restores hormonal modulation of adenylate cyclase activity in the hypothalamus and normalizes adenylate cyclase activation, which may improve cerebral activity [7]. Increasing ST content in the brain can be considered as an effective treatment for type 2 diabetes mellitus and its complications [11].

CONCLUSION

The pathophysiological aspects of DE are still far from being completely clear, and impaired neurotransmitter production can be considered as one of the possible hypotheses for the formation of this complication on the background of DM. DE will result in hyperactivation of the GABAergic, glutamatergic and dopaminergic systems, while the cholinergic and serotoninergic systems will be in a hypoactive state. Consequently, abnormally high values of such neurotransmitters as GABA, GT and DA, as well as low concentrations of other neurotransmitters, such as ACh and ST, may be early markers of DE formation, even at the preclinical stage

of DM. That is why the earliest possible diagnosis of DE by testing certain neurotransmitters will improve therapeutic approaches to manage this complication and improve the quality of life of patients with diabetes.

ADDITIONAL INFORMATION

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CHOOSING AN OPTIMAL METHOD FOR CONVERTING EPIDURAL ANALGESIA INTO ANESTHESIA DURING CESAREAN SECTION. LITERATURE REVIEW

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Abstract. ***Introduction.*** One of the key components of active labor management is effective pain management. Various methods of neuraxial analgesia (spinal, epidural anesthesia and their modifications) are widely used for analgesic purposes in obstetric practice. So, the question of choosing subsequent anesthetic tactics arises, if woman in labor with an epidural catheter already installed for analgesia purposes needs cesarean section for emergency indications. Conversion of epidural analgesia to anesthesia is one of the options for further anesthetic management. ***Goal of study:*** to determine the optimal method of converting epidural analgesia to anesthesia during emergency surgical delivery, based on scientific literature analysis. Those studies are discussed, in which various options of neuraxial anesthesia for labor pain relief and conversion of epidural analgesia to anesthesia when surgical delivery is necessary are used. ***Materials and methods.*** Inclusion criteria: original works published in peer-reviewed journals, availability of publication's full text. Exclusion criteria: lack of publication's full text, clinical cases, editorial articles, lack of data necessary for analysis. Conversion of labor epidural analgesia to anesthesia for caesarean section is a common procedure. For this, various local anesthetics (lidocaine, bupivacaine, ropivacaine, levobupivacaine, prilocaine, etc.) and adjuvants (adrenaline, sodium bicarbonate, etc.) are used. The time of sensory block onset, duration of motor block, speed of woman's recovery, hemodynamic stability and long-term obstetric and neonatal outcomes are used as efficiency criteria of successful conversion. But no single local anesthetic or combination of local anesthetics has shown clear superior benefits. The following are recognized as risk factors for unsuccessful conversion with varying levels of reliability: age of woman in labor, woman's height over 167 cm, gestational age (the higher it is, the greater is the likelihood of failure), lack of effective pain relief during labor, presence of breakthrough pain episodes, number of local anesthetic additional boluses, duration of labor analgesia, degree of caesarean section urgency and provision of anesthesia by a "non-obstetric" anesthesiologist. The risk of unsuccessful transition from epidural labor analgesia to anesthesia increases with the number of local anesthetic boluses administered during labor, degree of cesarean section urgency, duration of labor analgesia, and the provision of anesthesia by a "non-obstetric" anesthesiologist. ***Conclusion.*** To determine the optimal method of epidural analgesia conversion, choice of local anesthetic, its dosage, concentration and combinations of different drugs that do not have negative effect on the intrauterine state of fetus and newborn, further research is needed.

Keywords: epidural analgesia, conversion of epidural analgesia to anesthesia, cesarean section

ВЫБОР ОПТИМАЛЬНОГО МЕТОДА КОНВЕРСИИ ЭПИДУРАЛЬНОЙ АНАЛГЕЗИИ В АНЕСТЕЗИИ ПРИ КЕСАРЕВОМ СЕЧЕНИИ. ОБЗОР ЛИТЕРАТУРЫ

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Резюме. ***Введение.*** Одним из ключевых компонентов активного ведения родов является эффективное обезболивание. С анальгетической целью в акушерской практике широко применяют различные методики нейроаксиальной аналгезии (спинальная, эпидуральная анестезия и их модификации). Если роженице с уже установленным для аналгезии эпидуральным катетером по экстренным показаниям необходимо кесарево сечение, остро встает вопрос о выборе последующей анестезиологической тактики. Одним из вариантов дальнейшего анестезиологического обеспечения является конверсия эпидуральной аналгезии в анестезию. ***Цель исследования:*** на основе анализа научной литературы определить оптимальный метод конверсии эпидуральной аналгезии в анестезию при экстренном оперативном родоразрешении. Обсуждаются исследования, в которых использованы различные варианты нейроаксиальной анестезии для обезболивания родов, применение конверсии эпидуральной аналгезии в анестезию при необходимости оперативного родоразрешения. ***Материалы и методы.*** Критерии включения работ: оригинальные работы, опубликованные в рецензируемых журналах, наличие полного текста публикации. Критерии невключения: отсутствие полного текста исследования, клинические случаи, редакционные статьи, отсутствие данных, необходимых для анализа. Конверсия родовой эпидуральной аналгезии в анестезию при кесаревом сечении является распространенной процедурой. Для этого используются различные местные анестетики (лидокаин, бупивакаин, ропивакаин, левобупивакаин, прилокаин и др.) и адъюванты (адреналин, бикарбонат натрия и др.). В качестве критериев эффективности удачной конверсии применяются время наступления сенсорного блока, длительность моторного блока, скорость восстановления женщины, стабильность гемодинамики и отдаленные акушерские и неонатальные исходы. Но ни один из местных анестетиков или их комбинация не продемонстрировали однозначные непревзойденные преимущества. В качестве факторов риска неудачного выполнения конверсии с разным уровнем достоверности признаны: возраст роженицы, рост женщины более 167 см, срок беременности (чем он выше, тем вероятность неудачи больше), отсутствие эффективного обезболивания родов, наличие эпизодов прорывной боли, количество дополнительных болюсов местного анестетика, продолжительность обезболивания родов, степень срочности кесарева сечения, а также обеспечение анестезии «неакушерским» анестезиологом. Риск неудачного перехода от эпидуральной аналгезии родов к анестезии возрастает с увеличением количества болюсов местного анестетика, вводимых во время родов, степенью срочности кесарева сечения, продолжительностью обезболивания родов и оказанием помощи «неакушерским» анестезиологом. ***Заключение.*** Для определения оптимального метода конверсии

эпидуральной аналгезии, выбора местного анестетика, его дозировки, концентрации и комбинаций разных препаратов, не оказывающих отрицательного влияния на внутриутробное состояние плода и новорожденного, необходимы дальнейшие исследования.

Ключевые слова: эпидуральная аналгезия, конверсия эпидуральной аналгезии в анестезию, кесарево сечение

INTRODUCTION

Despite availability of numerous methods and schemes of analgesia and anesthesia in labor and abdominal delivery, the search for the safest one is still ongoing [1, 4, 11]. The last two decades were marked by an increased interest in neuraxial anesthesia methods (spinal, epidural anesthesia and their modifications), which, according to many authors, have a number of advantages and are optimal in obstetric practice [2, 14, 16, 19, 21, 21, 30, 33, 82].

From 2017 to 2018, 21% of more than 100,000 cesarean sections performed in England were carried out under epidural anesthesia [35]. Epidural analgesia is recommended by the World Health Organization as the primary method of labor pain relief, and 30% of women laboring in the UK and 60% in the US receive epidural analgesia [46].

The advantages of epidural analgesia are high analgesic efficacy, low complication rates, the possibility of adequate analgesic effect in the postpartum period, and conversion to epidural anesthesia when cesarean section is necessary [3, 5, 13, 36, 57, 65, 65, 92, 98].

When epidural analgesia is used during natural childbirth and situations require operative delivery (for both maternal and fetal indications), the anesthesiologist faces an issue of choosing an appropriate method of anesthesia. This issue depends on various factors, including urgency, mother's and fetus's health, since anesthesia may cause deterioration of uteroplacental and fetal blood flow, which predetermines the outcome of labor and affects a newborn in the early neonatal period [6, 49, 50, 68, 88].

It is known that different local anesthetics administered epidurally, as well as their combination in different concentrations have various effects both in labor and in the postpartum period. Thus, injection of lidocaine into epidural space is accompanied by the fastest development of motor block. Ropivacaine has a relative anesthetic efficacy of 0.6 compared to bupivacaine, is less cardiotoxic/neurotoxic and causes less pronounced motor blockade. Meanwhile, bupivacaine and levobupivacaine have almost the same anesthetic effect and cause dose-dependent motor block [8, 27, 46, 52, 78, 85].

The efficacy of epidural anesthesia for cesarean section does not depend on body mass index, but it can be influenced by height, the number of boluses of anesthetic administered during labor, duration of anesthesia, previous catheterization of epidural space, and other factors [31, 99].

Currently, there are no clear recommendations on converting epidural analgesia during labor to epidural anesthesia for emergency cesarean section. Various variants of neuraxial analgesia and primarily epidural analgesia are widely used worldwide to anesthetize natural childbirth. In the USA, more than 70% of women in labor prefer adequate anesthesia for labor [56].

Disputes about analgesia and its outcomes are probably the most acute issue in the history of obstetric anesthesiology. However, providing effective analgesia is one of the key components of active labor management, and its use is recommended in modern protocols [7, 9, 56].

A population-based study of 575,524 women who underwent their first delivery through natural labor in New York City obstetrics facilities from 2010 to 2017 was conducted. The use of neuraxial analgesia reduced the risk of severe maternal complications by 14%, mainly by reducing postpartum hemorrhage, and the number of these complications was independent of premorbid background and race or ethnicity [44].

Efficiency of analgesia, among other factors, is influenced by the method of anesthetic delivery. Currently, bolus, continuous infusion, patient-controlled epidural analgesia (PCEA) and computer integrated patient-controlled epidural analgesia (CIPCEA), as well as various combinations of these delivery modes are widely used [18, 46, 63, 86]. Each has its own pros and cons [39, 67, 95].

Although epidural analgesia is the most effective method of anesthesia [53, 97], there is a problem described in earlier studies. They showed that epidural analgesia increased the likelihood of operative delivery by caesarean section [37, 83]. However, the 2005 Cochrane Review, which compared epidural analgesia with other methods of analgesia or labor without analgesia, showed no impact of epidural analgesia (EA) on the incidence of cesarean section [20]. It has been demonstrated that 28% of women who were anesthetized with epidural analgesia delivered by cesarean section compared to 31.7% of women who were not anesthetized [53]. Later work has shown a lower cesarean section rate of 4–14% when epidural analgesia is used to anesthetize labor [56].

Neuraxial analgesia in natural childbirth is not a universal procedure, so the techniques used for its implementation may vary in different countries and institutions, which, in turn, may affect the influence of EA on a cesarean section rate [51].

When cesarean section is indicated, the presence of an epidural catheter placed for analgesia may be used for further anesthesia. In this situation, choosing a method of anesthetic support is based on urgency of surgery, anesthesiologist's experience and personal preference.

When it is necessary to convert epidural analgesia to anesthesia, a higher dose of concentrated local anesthetic is injected into the epidural catheter, which allows epidural analgesia to be considered the optimal technique for anesthesia of labor [25, 56]. For this purpose, various local anesthetics are used, and adjuvants such as sodium bicarbonate, adrenaline, and narcotic analgesics are added to enhance the effect of local anesthetics and lead to a faster development of persistent sympathetic blockade [35, 60]. Based on a survey of UK anesthesiologists, 13 combinations of local anesthetics and adjuvants that are used for this purpose have been identified [84].

At the same time, it should be emphasized that injection of narcotic analgesics during neuraxial anesthesia is limited in Russia. Only promedol and morphine are allowed to be administered in the epidural space, while intrathecal administration of narcotic analgesics is not recommended [2]. Moreover, mixing of drugs in an emergency situation may lead to drug dosing errors and delay the time of local anesthetic administration [42, 93].

The choice of local anesthetics and the options for combining them with adjuvants differ from country to country. Thus, the survey of anesthesiologists in the United Kingdom showed that 40% of specialists used only 2% lidocaine hydrochloride solution or its combination with other narcotic analgesics, 72% of respondents used levobupivacaine or bupivacaine [38, 84, 90, 93].

No difference was found in sensory block onset time to the Th_7 level when comparing the use of a mixture of 2% lidocaine solution with adrenaline 1:200,000 and 0.5% bupivacaine hydrochloride solution with 50 μg fentanyl [42].

It has been demonstrated that there is no difference in sensory block time to Th_4 when 0.75% ropivacaine hydrochloride and 0.5% bupivacaine hydrochloride are used [90].

Using a single drug, such as ropivacaine or levobupivacaine, appeared to be more preferable since it reduced the number of errors and the time required to dilute it. This may be clinically significant in emergency situations, such as fetal distress [15, 93]. In other non-life-threatening cases, few more minutes spent on preparing a solution for insertion is not relevant [43, 93].

A prospective, randomized, double-blind, double-center controlled clinical trial compared equipotent doses of intrathecal hyperbaric prilocaine 50 mg or hyperbaric bupivacaine 10 mg, and both drugs in combination with sufentanil 2.5 μg and morphine 100 μg for planned cesarean section. An epidural catheter was placed as a backup, in case spinal anesthesia failed. Median motor block time was significantly shorter in the hyperbaric prilocaine group (110 [104–150] min vs 175 [135–189] min, p=0.001). The woman's first unassisted movement was achieved earlier in the prilocaine group (204.5 [177–246.5] min vs 314 [209.25–400] min, p=0.007), and the incidence of arterial hypotension was significantly higher with bupivacaine (p=0.033). No additional epidural analgesia was required. The authors conclude that prilocaine provides shorter motor block, faster recovery and hemodynamic stability than bupivacaine, while providing equivalent depth of anesthesia [41].

It has been shown that 93.5% of cesarean sections were performed under neuroaxillary anesthesia, and 41% of patients had epidural catheters inserted earlier during labor. These catheters were subsequently used to provide anesthesia for cesarean section [73, 93].

Conversion of epidural analgesia to anesthesia for cesarean section is necessary but not always successful [47, 56, 69].

The ineffectiveness of conversion of epidural analgesia to anesthesia for emergency cesarean section ranges from 0 to 21% [65, 69].

The incidence of failed conversion is recorded as a complication. It is included in the quality of care audit, subsequently analyzed in detail, and depends on many factors. The Association of Anesthesiologists in the United Kingdom recommends that the rates of failed conversion should not exceed 1% for planned caesarean section and 5% for emergency caesarean section [56, 69].

Factors for failed epidural conversion include maternal age [56, 71], woman's height greater than 167 cm [56, 69], gestational age (the greater it is, the higher the likelihood of failure) [56, 71], lack of effective labor analgesia, presence of episodes of breakthrough pain [28, 56], number of additional boluses of local anesthetic, duration of labor analgesia [56], degree of urgency of cesarean section [56, 60], and anesthesia factors such as epidural analgesia without CA [56], as well as provision of anesthesia by a "non obstetric" anesthesiologist [28, 56, 87]. Taking into account the above-mentioned factors, the most important are labor anesthesia by a "non-obstetric" anesthesiologist, a large number of additional boluses of local anesthetic, and the degree of urgency of cesarean section [56, 69].

Crucial factors that influence the choice of anesthesia technique during labor include time required for sensory

block to develop and the urgency of cesarean section. These factors may partially explain the fact that most anesthesiologists choose not to manipulate a catheter or substitute epidural anesthesia. Further administration of local anesthetic may, in addition, increase the risk of systemic toxicity [10, 17, 56, 74].

Risk factors associated with failed conversion of epidural anesthesia have been widely studied. Breakthrough pain in labor may be a marker of poorly functioning epidural analgesia or indicate discoordinated labor [56, 75].

To date, there is no clear consensus on the effect of body mass index (BMI), the degree of cervical opening at the time of initiation of epidural analgesia, and the administration of combined spinal-epidural versus standard epidural analgesia techniques. However, the duration of epidural analgesia in labor has been shown to significantly increase the likelihood of unsuccessful epidural conversion for cesarean section [35, 69].

A literature review revealed controversial data regarding body mass index and the number of successful conversions of epidural analgesia to anesthesia [23, 69]. A meta-analysis that included 6 studies showed that maternal weight was not associated with the efficacy of epidural conversion [24]. Only one of 6 studies demonstrated an association between body weight and failed epidural conversion [71].

Obese women have higher cesarean section rates, are more likely to be diagnosed with difficult airway and have more complications when performing a neuraxial block. This should prompt more careful monitoring and careful management of epidural analgesia in labor. Greater thickness of soft tissue between skin surface and yolk ligament increases the likelihood of catheter displacement in an obese patient during movement [24, 59, 87].

Currently, there is no conclusive evidence that duration of epidural analgesia in labor (brief or prolonged) is a risk factor for unsuccessful conversion to epidural anesthesia. It has been suggested that prolonged labor may result in catheter dislodgement from the epidural space. Conversely, when indications for cesarean section are established immediately after induction of labor anesthesia, there may not be enough time to determine the efficacy of anesthesia for cesarean section. Most authors studying this problem have failed to prove the relationship between the duration of epidural analgesia and the success of conversion [56, 69].

In case the causes of ineffective epidural conversion are identified and this technique is improved according to the analysis of failures, this may prevent the use of more complex and costly methods of anesthesia. Violation of the epidural conversion technique may require conversion to general anesthesia [91].

There are many reasons why general anesthesia is undesirable, including higher incidence of maternal mortality, possibility of pulmonary aspiration, difficult tracheal intubation, neonatal depression, uterine hypotension with volatile anesthetics, postoperative pain, and nausea [27, 56]. Maternal dissatisfaction and pain are leading causes of litigation related to obstetric anesthesia [32, 66, 69].

Definitions of epidural conversion failure are contradictory. Most authors define failure as conversion to general anesthesia [69]. Other authors define failure as conversion to another form of anesthesia [69, 87].

Most anesthesiologists (89%) would consider supplementing the epidural analgesia for further cesarean section. When analyzing whether to supplement existing epidural analgesia of labor, factors influencing the decision were the efficacy of epidural analgesia in labor (99%), the degree of urgency of cesarean section (73%), and the level of sensory blockade (61%).

Anesthesia options include the following: manipulation of the epidural catheter (pull up 0.5–1 cm) or its replacement, performance of combined spinal-epidural or spinal anesthesia, and induction of general anesthesia [35].

In addition to epidural analgesia without dura puncture, labor can be anesthetized by combined spinal-epidural analgesia (CSEA), in which the dura is punctured with a small-gauge spinal needle. There is evidence that CSEA-initiated labor analgesia is more effective in anesthetizing the labor pain [54, 69, 72]. At the same time, a retrospective study including 1,025 laboring women compared epidural with combined spinal-epidural analgesia, where they demonstrated a higher rate of failed conversion with EA compared to CSEA [64]. The CSEA technique allows better identification of the epidural space and subsequent catheter placement, and the puncture hole in the dura improves local anesthetic penetration and thus improves the quality of anesthesia [24, 76].

Other investigators have failed to demonstrate a difference between epidural and combined spinal-epidural analgesia [40, 69].

Thus, combined spinal-epidural analgesia is more reliable as a method of labor analgesia, although there is currently insufficient data to conclude that CSEA is superior to EA for conversion in case of cesarean section. Several studies have shown that neuraxial methods of labor analgesia performed by obstetric anesthesiologists reduces the likelihood of failed epidural conversion [55, 87].

There are 2 out of 70 reported cases of failed conversion after epidural catheter placement performed by an obstetric anesthesiologist compared to 20 out of 170 cases of catheterization performed by a “non-obstetric” anesthesiologist. The obstetric anesthesiologist has been shown to be more successful because he or she can manipulate the epidu-

ral catheter with greater confidence or use other neuraxial anesthesia techniques to avoid the need for general anesthesia [55, 87].

According to Campbell D.C. et al. (2009), the incidence of general anesthesia was 5.5% when the conversion was performed by a "non-obstetric" anesthesiologist compared to 1.2% when the manipulation was performed by an obstetric anesthesiologist. Other authors have shown that failure rates of conversion amounted to 7.2 and 1.6%, respectively [40, 69].

It might be explained by more correct manipulations with an epidural catheter in obstetric patients by obstetric anesthesiologists. It has been demonstrated that 84.6% (22 of 26) of poorly functioning epidural catheters can be successfully repaired by pulling up 1 cm, as evidenced by a pronounced anesthetic effect after such a manipulation. It has been shown that 58.3% of obstetric anesthesiologists use this technique, while only 5.9% of "non-obstetric" anesthesiologists did so [28]. The overall failure rate of epidural anesthesia conversion is also confirmed by other authors [29, 56, 58].

Several studies have reported that additional boluses of local anesthetic required to treat breakthrough pain during epidural analgesia are associated with a higher failure rate of epidural anesthesia conversion [42, 84]. Even a single unplanned bolus increases the likelihood of epidural conversion failure. Quantity of boluses was the best predictor of ineffective conversion from epidural analgesia to anesthesia [28, 69].

A meta-analysis showed that the rate of ineffective epidural conversion increased 3-fold in laboring women who required additional boluses during labor [24].

The degree of emergency cesarean section is also associated with failed epidural conversion. Up to 25% of epidural conversion failures were identified when cesarean section was performed immediately upon the development of fetal life-threatening conditions [48, 56, 69, 77, 81]. The urgency for surgery is related with ineffective epidural conversion. This convertion cannot always be achieved in a few minutes designated for a cesarean section for vital indications. General anesthesia allowed to start surgery on average 8 minutes faster than regional anesthesia [26, 69].

Thus, urgency of cesarean section determines the ineffectiveness of epidural conversion. Nevertheless, it is well known that general anesthesia is often preferred when time is critical.

Attempting to convert epidural analgesia to anesthesia, it is advisable to determine the level of sensory block by needling the skin above Th_5–Th_6, there should be a loss of perception as well as disappearance of cold sensation at Th_3 soon after injection of local anesthetic into the epidural catheter [69, 93]. If a surgical stage of anesthesia cannot be achieved, then a anesthesiologist switches to alternative methods such as different variants of neuraxial anesthesia or general anesthesia. An unsuccessful attempt to convert epidural analgesia into anesthesia when cesarean section is required poses a difficult clinical problem to an anesthesiologist, since it is necessary to choose the most optimal method of anesthesia.

Epidural anesthesia. After a failed epidural conversion, it is possible to insert a new catheter into the epidural space. Lee S. etal. reported that 21 of 1025 catheters were replaced during labor before cesarean section. In all cases of replacement, epidural analgesia was successfully converted to anesthesia for operative delivery [53, 64, 94].

However, epidural catheter replacement is time-consuming. Careful titration of local anesthetic to achieve surgical stage of anesthesia should be kept in mind, as repeated injection of a full dose of local anesthetic into the epidural space may lead to the development of systemic toxicity as a result of possible catheter migration as well as other complications [10, 69].

Spinal anesthesia. Spinal anesthesia for cesarean section may be used after epidural analgesia and is performed more frequently because of inadequately functioning epidural analgesia, either immediately before attempted epidural conversion or after failed epidural conversion. The decision to initiate spinal anesthesia after epidural analgesia for labor remains controversial and should be undertaken with caution. Spinal access involves removal of the epidural catheter and repeat puncture for spinal anesthesia. Spinal anesthesia is preferred by some practitioners who believe it may provide better anesthesia compared to epidural anesthesia [69].

Traditionally, the initiation of spinal anesthesia shortly after discontinuation of epidural anesthesia during labor has not been encouraged because of numerous reports of subsequent development of high or total spinal block [35, 69]. The local anesthetic (LA) dose should be reduced to lower the risk of complications when spinal anesthesia is initiated shortly after an unsuccessful epidural conversion attempt. The local is injected into the spinal space. It is also possible to sustain a pause between the last injection of local anesthetic into the epidural catheter and the spinal space [69].

More than one-third of anesthesiologists have experienced the development of high or total spinal block during spinal anesthesia, but these complications have been reported almost nine times less frequently during CSEA [35, 62].

The optimal dose of local anesthetic for spinal anesthesia after epidural analgesia for labor is unknown. Some studies suggest that decreasing the dose of anesthetic may

adversely affect efficacy of the anesthesia administered. This results in an increased need for intravenous or inhaled anesthetics required for general anesthesia [69].

Combined spinal-epidural anesthesia. CSEA has become widespread in anesthesia practice and is widely used not only in obstetrics, but also in general surgery, traumatology-orthopedics, urology, gynecology and so on. Rapid onset and prolonged effect of anesthesia, the possibility of continuing anesthesia in the postoperative period are the main advantages of CSEA over spinal and epidural anesthesia [12].

This method of anesthesia is an attractive option after unsuccessful epidural conversion because it provides rapid onset, reliable anesthesia, and the possibility of prolonging the blockade by additional injection of local anesthetic into an epidural catheter [69]. When performing combined spinal-epidural anesthesia, a deliberately low dose of local anesthetic is first injected into the subarachnoid space, such as 6–9 mg of 0.75% hyperbaric bupivacaine, which reduces the risk of developing a high spinal block. If the resulting block is not enough for a surgical stage of anesthesia, additional doses of local anesthetic can be administered through a newly placed epidural catheter [69].

Some authors report a longer time required to perform CSEA compared to EA, although only one trial showed a clinically significant difference which amounted to 11 minutes [62]. Specialists have expressed concern regarding an untested epidural catheter when initiating a cesarean section under CSEA. After administering a small dose of LA intrathecally, subsequently inserted LA may increase anesthetic distribution in the spinal canal, thereby increasing the likelihood of sensory block development [69].

Extended spinal anesthesia. Extended spinal anesthesia has long been considered the best option, especially for patients with cardiopulmonary disease, where the level of sensory block must be carefully monitored [69]. Extended spinal anesthesia is also indicated for patients in other categories, such as vertebral neurology, obesity, and anticipated difficult tracheal intubation [69]. However, the likelihood of headache after dura mater puncture with a large-diameter needle remains high [69].

Spinal anesthesia can be unsuccessful in a number of cases. There are many ways to define the term “failed spinal anesthesia” Many publications indicate two main points. First, partial failure is defined as pain or discomfort occurring during surgery and requiring additional intravenous or inhalation analgesia [22]. Second, complete failure is defined as failure to achieve adequate sensory blockade, making it necessary to perform general anesthesia [89]. The incidence of complete failure of spinal anesthesia requiring conversion to general anesthesia for caesarean section ranges from 0.5 to 6.4% [79].

In addition, extended spinal anesthesia may be associated with the development of neurological complications [34, 69]. For these reasons, extended spinal anesthesia is used in patients who experienced unintentional puncture of dura mater during catheterization of the epidural space.

Local anesthetic infiltration. Local anesthetic infiltration has been used in past when neuraxial anesthesia or general anesthesia was not performed. This method of anesthesia is not currently used, mainly due to lack of training and experience, resulting in inadequate anesthesia, and the possibility of delayed care. However, local anesthetic infiltration can be used in an emergency situation to augment inadequately functioning neuraxial anesthesia [69, 80]. Up to 10.7% of patients during caesarean section experience discomfort or anxiety after conversion of epidural anesthesia from analgesia, requiring additional administration of intravenous and/or inhaled anesthetics [69, 80].

General anesthesia. Neuraxial anesthesia is usually more preferable than general anesthesia because it allows a mother to participate in labor, reduces the likelihood of intubation problems with difficult airways, and avoids depressive effects of systemic anesthetic drugs on a fetus and uterine tonus. It is also possible to preserve woman’s consciousness during general anesthesia. At the same time, the use of neuraxial anesthesia facilitates postoperative analgesia [24, 61].

Switching to general anesthesia and avoiding the use of an epidural catheter for a surgical stage during CS is considered an inefficient option for using regional anesthesia [53, 96].

Many specialists prefer to perform general anesthesia during emergency caesarean section due to fetal deterioration without any attempt to pre-convert epidural analgesia to anesthesia [28, 61, 94].

This approach may be based on the notion that it takes less time to induce general anesthesia than to convert epidural analgesia to anesthesia. E. Palmer et al. (2018) demonstrated a significantly shorter time interval from induction to incision with general anesthesia, which was 6 minutes compared to 11 minutes with epidural anesthesia, but this time difference did not correlate with worse neonatal outcomes [72]. On the contrary, the use of general anesthesia is associated with lower Apgar scores five minutes after delivery, the need for mask ventilation and neonatal admissions to intensive care units [35, 70, 96].

Back in 2007, P. Popham et al. showed that there was no significant difference in time taken from the indication for caesarean section to fetal delivery regarding general and epidural anesthesia, which amounted to 17±6 min and 19±9 min, respectively [77].

General anesthesia has been associated with preservation of consciousness during surgery and complications related to aspiration and failed intubation, as well as critical incidents after conversion of regional anesthesia rather than primary conversion to general anesthesia [74, 96].

A major achievement described by S. Ismail et al. (2015) was the reduction of rejections to perform conversion. This was evidenced by performing general anesthesia in 40.3% of cases without attempting to convert epidural analgesia to anesthesia when performing caesarean section. Emergency caesarean section was the main reason for rejecting the use of epidural anesthesia conversion in 50 (28.4%) women. Previously, authors described the use of general anesthesia as the main method of anesthetic management without any attempt to convert epidural analgesia to anesthesia due to the urgency of caesarean section [47, 53].

Conversion of epidural analgesia for labor to anesthesia for caesarean section is an important strategy to limit the use of general anesthesia in obstetrics. A high rate of successful conversions presents a good criterion for quality of care, indicating the prior availability of functional epidural analgesia as well as the avoidance of general anesthesia [24, 45].

Strategies aimed at improving the conversion will enhance safety and quality of anesthetic care provided in obstetrics.

CONCLUSION

Epidural analgesia in labor is presented as the most effective method of relieving labor pain, which can be converted to epidural anesthesia in case of emergency caesarean section, as an existing epidural catheter might be used to administer local anesthetics. The optimal method of epidural analgesia conversion that does not adversely affect the intrauterine condition of the fetus and neonate has not been determined to date. The risk of unsuccessful conversion from epidural analgesia to anesthesia increases with the number of boluses of local anesthetic administered during labor, the degree of urgency of caesarean section, the duration of anesthesia, and the assistance provided by a “non-anesthesiologist”.

When epidural conversion fails, the use of spinal or combined spinal-epidural anesthesia is preferred over general anesthesia. There is no unambiguous approach in selecting a local anesthetic, its dosage, concentration and combination with different drugs when converting epidural analgesia to caesarean section anesthesia, which requires further research.

ADDITIONAL INFORMATION

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

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MOLECULAR GENETIC ASPECTS OF CORNEAL TISSUE REPAIR

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Abstract. The article is devoted to a scientific literature review on the issues of reparative histogenesis and cell differentiation in the cornea at the genetic level. The most vulnerable membrane in case of eye injuries is the cornea. In this regard, the assessment of its regeneration processes, including at the molecular genetic level, becomes important. Knowledge of the molecular biology of regenerative genes is far from complete, and many aspects remain insufficiently studied. The genes *MKI67, TAB3, PAX6* are involved in the regeneration of corneal tissue, including after injury. This review focuses on these three genes. Ki-67 protein is a universal marker of proliferation and is necessary for maintaining the cell cycle. Pax-6 is an early marker of corneal epithelial cell differentiation. Expression of this gene is suppressed in many tissues of an adult, but it persists in eye cornea, participating in the normal functioning of the cornea. *TAB3* gene, as a correlate of TGF-β activation, helps to increase the intensity of proliferation and migration of epithelial cells and promotes rapid healing of the wound surface. Currently, the study of the patterns of cyto- and histogenesis, differentiation of cells and tissues of the organ of vision, their physiological and reparative regeneration and the regulation of these processes at the molecular genetic level in the aspect of regenerative medicine is being updated.

Keywords: regeneration, cornea, gene expression

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ АСПЕКТЫ РЕПАРАЦИИ ТКАНЕЙ РОГОВИЦЫ

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Резюме. В статье приводится обзор научной литературы по вопросам репаративного гистогенеза и дифференцировки клеток в роговице на генетическом уровне. Наиболее уязвимой оболочкой при травмах глаза является роговица. Важное значение приобретает оценка процессов ее регенерации, в том числе на молекулярно-генетическом уровне. Знания о молекулярной биологии регенераторных генов далеки от полноты, и многие аспекты остаются недостаточно изученными. В регенерации тканей роговицы, в том числе после травмы, принимают участие гены *MKI67, TAB3, PAX6*. В данном обзоре делается акцент на этих трех генах. Белок Ki-67 — универсальный маркер пролиферации, необходим для поддержания клеточного цикла. Pax-6 — ранний маркер дифференцировки эпителиальных клеток роговицы. Экспрессия данного гена подавляется во многих тканях взрослого человека, но она сохраняется в роговице глаза, участвуя в нормальном ее функционировании. Ген *TAB3* как коррелят активации TGF-β способствует увеличению интенсивности пролиферации

и миграции эпителиоцитов, содействует быстрому заживлению раневой поверхности. В настоящее время актуализируется изучение закономерностей цито- и гистогенезов, дифференцировки клеток и тканей органа зрения, их физиологической и репаративной регенерации и регуляции этих процессов на молекулярно-генетическом уровне в аспекте регенеративной медицины.

Ключевые слова: регенерация, роговица, экспрессия генов

The determining factor in development and functional specialization of tissues is the genetic determination and subsequent differentiation. During the normal course of development, in competent material, under the influence of one or another inducer, initially unstable (labile) determination occurs, and later, irreversible (stable) determination starts [5]. Only after this the rudiment of a certain tissue appears. The tissue determination of cornea is based on the expression of certain tissue-specific genes that determine the synthesis of nucleic acids and proteins [4].

During reparative histogenesis, it is often necessary to observe coordinated gene expression when several specific protein substrates are synthesized in cells or when some humoral factor induces the expression of several genetic loci in cells of different tissue types.

When studying corneal regeneration, it is necessary to dwell on some genes whose action has been described and plays a key role in the development and differentiation of tissues of the eye's anterior segment.

Ki-67 was originally identified as an antigen recognized by a monoclonal antibody generated by immunizing mice with nuclei isolated from the Hodgkin lymphoma cell line L428 [16]. Cloning and sequencing of complementary deoxyribonucleic acid (cDNA) of Ki-67 [15, 37] revealed that the amino acid sequence had little similarity to other known proteins, so the protein was named after the antibody that identified it. Ki originates from Kiel, Germany, where the antibodies were developed, with 67 being the well number on a 96-well plate. In 1996, the entire *Ki-67* gene locus was sequenced and was found to contain approximately 30,000 bases [41].

The *MKI67* gene, encoding a Ki-67 protein, is a universal marker of proliferation and is detected in cells in all phases of the mitotic cycle except G0 [1]. The Ki-67 protein is also necessary for maintaining the cell cycle.

A disadvantage of the MKI67 gene determination method is that mitosis is the fastest phase of cell cycle, which may lead to an underestimation of actual values of its quantity [12]. The protein half-life is approximately 90 minutes [19], so inhibition of protein synthesis for 60 minutes leads to a significant decrease in the Ki-67 protein level [6].

Average messenger ribonucleic acid (mRNA) and Ki-67 protein levels in proliferating cells appear to be independent of cell type. Similar levels of RNA and protein are observed in several human cell lines [30].

Ki-67 expression is a useful marker of early precancerous lesions [7]. Experimental studies have confirmed changes in Ki-67 expression in the eye.

Thus, when exposed to a femtosecond laser (a system capable of generating ultra-short laser pulses lasting 5 femtoseconds or more) on cornea, the Ki-67 expression increases on the first day and reaches a maximum in epithelial cells on the third day [29].

In early stages of corneal damage, cells with high Ki-67 expression are localized predominantly in the region of the growth zone of limbus [3].

In a study of pterygium, it was found that Ki-67 expression increased and depended on the duration of a disease, but did not depend on the extent of spread to cornea and the severity of a disease [22]. It was found that the number of immunopositive cells to Ki-67 in epithelial layer of pterygium is significantly higher than in the normal conjunctiva bordering the cornea [26]. In normal conjunctiva, Ki-67 expression is <5% [27].

In 1991, the PAX6 gene was identified in humans on the short arm of chromosome 11 in the 11p13 region [40]. Pax-6 is an early marker of corneal epithelial cell differentiation [24]. The PAX6 gene is a critical regulatory gene that encodes a specific DNA-binding transcription factor capable of initiating eye development during embryogenesis [20, 42].

PAX6 expression is downregulated in many adult tissues, but it is retained in the adult cornea [23], indicating that PAX6 is required not only for ontogenesis but also for normal corneal function [14], where the cornea is involved in wound maintenance and healing [10, 25].

PAX6 supports the regeneration process by providing differentiation of human corneal epithelial cells [22]. At the same time, the *PAX6* gene plays a key role in maintaining the multipotent state of several types of cells (iris, retinal pigment epithelium, and neuronal retina). This combination of regulatory functions is explained by the presence of different functional domains in its structure [2].

In adults, the PAX6 protein is responsible for maintaining the pool of stem cells in the lens epithelium, corneal limbus, pigment epithelium of the ciliary body and iris [28].

Transcriptome analysis (RNA-seq) of corneal epithelium from mouse embryos confirmed that PAX6 was relatively highly expressed in corneal epithelium, indicating a key role of PAX6 in the development of this cell layer [36].

PAX6 has been identified as a key molecular factor capable of reprogramming rabbit skin epithelial cells to give rise to corneal epithelial cells and repair corneal surface defects [34]. In studies on rabbits, PAX6 has been identified as a cellular molecular factor capable of reprogramming rabbit skin epithelial cells, trans-differentiating them into corneal-like epithelium, and repairing corneal surface defects.

It has been shown that changes in PAX6 expression, both downward and upward, affect cell differentiation, erosion healing response, and corneal transparency [11].

Transforming growth factor beta (TGF-β) is a widely studied cytokine that is synthesized in virtually all cells and tissues of the body.

Expression of the TAB3 gene was considered as a correlate of TGF-β (transforming growth factor beta) activation, which, under conditions of corneal trauma, promotes an increase in the intensity of proliferation and migration of epithelial cells, which contributes to rapid healing of the wound surface [32].

TGF-β cytokines were first discovered in the early 1980s, and three TGF-β isoforms have been identified in mammals (TGF-β1, TGF-β2, and TGF-β3) [17].

TGF-β 1, 2 and 3 have been detected in the aqueous and vitreous humor of a human eye [4, 8]. In addition, these ligands are also expressed in cornea, ciliary epithelium, lens, retina and blood vessels [9].

Depending on the cellular context, TGF-β family members can either inhibit or stimulate proliferation, control extracellular matrix turnover, and participate in epithelial-mesenchymal interactions during embryogenesis. Their activity is also associated with tissue repair and modulation of immune response [18].

An integrated process of cell proliferation, migration, differentiation, desquamation, and apoptosis maintains homeostasis of the adult corneal epithelium, but alterations in these processes result in persistent corneal abnormality and may lead to blindness. TGF-β is usually restricted to healthy intact corneal epithelium [39]. In the injured cornea, TGF-β1 is weakly expressed, while TGF-β2 is expressed. M.I. Huh et al. [21] reported differences in TGF-β3 levels after corneal injury in chickens. TGF-βRI and II are also expressed in the injured stroma, thus participating in the wound healing process in corneal tissue [43]. Following corneal injury, overexpression of TGF-β protein leads to an increase in profibrotic factors and pro-inflammatory cytokines.

Taken together, these observations support a stimulatory role for TGF-β family members in the corneal wound healing process, indicating that they may represent therapeutic targets for the treatment of corneal injury.

TGF-β family proteins that transmit signals through the SMAD pathway (SMAD proteins are signal transducers and transcriptional modulators that mediate several signaling pathways) are likely essential for maintaining corneal epithelial homeostasis [35]. Thus, blocking TGF-β activity at the level of SMAD signaling has been proposed as a treatment option to accelerate corneal wound healing. Indeed, blocking TGF-β protein activity by in vivo gene transfer of soluble TGF-β receptor type RII accelerates corneal injury tissue repair in rats. Blocking TGF-β activity by adenoviral gene transfer of soluble TGF-β receptor type RII results in inhibition of corneal opacification, edema, and angiogenesis [31]. The use of a TGF-β receptor inhibitor (SB431542) also maintains normal endothelial phenotypes in cultured corneal endothelial cells [33].

Monoclonal antibodies are potential treatments for corneal scarring: TGF-β antagonists such as antibodies to TGF-β1 and -β2 have been shown to inhibit cutaneous scar formation in rodent wounds [38]. The use of tranilast, a TGF-β inhibitor, reduced the recurrence of corneal fibrosis or primary pterygium, a degenerative disease of the ocular surface with fibrovascular growth of the bulbar conjunctiva onto the cornea [13].

Thus, there is currently a trend towards optimizing the processes of determining priorities for basic research, including in ophthalmology. This concerns the study of the patterns of cyto- and histogenesis, differentiation of cells and tissues of the visual organ, their physiological and reparative regeneration and regulation of these processes at the molecular-genetic level. In this regard, the given, obviously incomplete, list of genetic markers of elementary histogenetic processes of the structural elements of the cornea will be an objective methodological basis for evidence-based ophthalmology.

ADDITIONAL INFORMATION

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

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

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PHYSIOLOGICAL ROLE OF GLUTATHIONE IN THE HUMAN BODY (LECTURE)

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Abstract. Glutathione tripeptide is a small thiol molecule, which protects the body from reactive oxygen forms, aging, exposure to xenobiotics, destructive inflammation, various forms of cell death, and many diseases that are the leading causes of mortality worldwide. Glutathione is found in all animal cells. It ensures optimal performance under the effect of various adverse environmental factors. The report gives an overview of the structure and synthesis of glutathione in the body, its key role in the formation of antioxidant protection, detoxification of exogenous and endogenous xenobiotics. We discuss the participation of the glutathione system in the innate and acquired immune response processes, programmed cell death, cell proliferation, DNA repair and synthesis. The article provides a list of factors that cause glutathione system depletion followed by a decrease in the reserve capacity of the cell, up to its death. The content of glutathione in food products and the possibility of its transport into the internal environment from food are discussed. Changes in the content of glutathione depending on the methods of its introduction into the body are considered. The objective was to provide the variety of physiological aspects of the role of glutathione, to give a complex impression of the importance of this molecule for the body, to demonstrate the significance and possibility of preventing depletion of the glutathione system.

Keywords: glutathione, antioxidant, glutathione peroxidase, detoxification, glutathione transferase, glutathione transporters, disease prevention

ФИЗИОЛОГИЧЕСКАЯ РОЛЬ ГЛУТАТИОНА В ОРГАНИЗМЕ (ЛЕКЦИЯ)

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Резюме. Трипептид глутатион — небольшая тиольная молекула, защищающая организм от активных форм кислорода, старения, воздействия ксенобиотиков, разрушительного воспаления, различных форм клеточной смерти, многих заболеваний, являющихся ведущими причинами смертности во всем мире. Глутатион содержится во всех животных клетках, обеспечивая оптимальное функционирование в условиях воздействия различных неблагоприятных факторов внешней среды. В лекции рассматриваются строение и синтез глутатиона в организме, его ключевая роль в формировании антиоксидантной защиты, в обеспечении детоксикации экзогенных и эндогенных ксенобиотиков. Обсуждается участие системы глутатиона в протекании процессов врожденного и приобретенного иммунитета, запрограммированной клеточной смерти, в пролиферации клеток,

в процессах репарации и синтеза ДНК. Приводится перечень факторов, которые способны истощать систему глутатиона, что сопровождается снижением резервных возможностей клетки, вплоть до гибели. Обсуждается содержание глутатиона в продуктах питания и возможности транспорта его во внутреннюю среду из пищи. Рассматриваются изменения содержания глутатиона при различных способах его введения в организм. Автор ставил перед собой задачу показать читателю многообразие физиологических аспектов роли глутатиона, дать целостную картину значимости этой молекулы для организма, продемонстрировать важность и возможность профилактики истощения системы глутатиона.

Ключевые слова: глутатион, антиоксидант, глутатионпероксидаза, детоксикация, глутатионтрансфераза, транспортеры глутатиона, профилактика заболеваний

INTRODUCTION

Glutathione is a water-soluble tripeptide formed from the residues of three amino acids: glutamic acid, cysteine and glycine. Glutathione is found in many plant, microbial and animal cells. A decrease in its intracellular content is an important factor in the development of aging, Alzheimer's disease, Parkinson's disease, autism, schizophrenia, cataract, macular degeneration, glaucoma, osteoporosis, carcinogenesis, coronary heart disease, hemorrhagic and ischemic stroke, atherosclerosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), bronchial asthma, cystic fibrosis, immunodeficiency, viral infections and diabetes mellitus [3, 5, 14, 20, 21].

The molar concentration of glutathione in animal cells (1–10 mM) is higher than the concentration of most organic substances [4]. Glutathione is synthesized in the cytosol, and is also found in the nucleus, mitochondria, and endoplasmic reticulum, where it enters via intracellular transport [53]. Liver provides up to 90% of all circulating glutathione and is called the main organ of glutathione synthesis [48].

Cytosolic GSH synthesis occurs via two ATP-dependent reactions. The first reaction is catalyzed by glutamate-cysteine ligase (also known as gamma-glutamylcysteine synthetase), which combines glutamate and cysteine. Regulation of the activity of this enzyme is carried out, firstly, by competitive inhibition by glutathione according to the negative feedback principle, and secondly, by the availability of cysteine [4]. The physiological concentration of cysteine in the cell is significantly lower than the concentration of glutamate. With a dietary deficiency of amino acids, a decrease in the level of glutathione in blood plasma is recorded, and with an increase in the intake of cysteine into the body, the level of glutathione increases [32].

STRUCTURE AND BIOLOGICAL FUNCTION

Glutamate-cysteine ligase consists of two subunits encoded by different genes. Their expression is induced by the action of active forms of oxygen and nitric oxide, physical inactivity, pro-inflammatory cytokines, lycopene, beta-carotene, and vitamin D [4, 19, 44].

Being the smallest intracellular thiol molecule, glutathione has a high reducing ability, providing antioxidant protection to the body.

Glutathione (GSH) is a hydrogen donor. Each of two GSH molecules donates a hydrogen atom to form a dimer (GSSG), which is the oxidized form of glutathione: $2GSH \rightarrow GSSG + 2H\bullet$. Concentration of GSSH in tissues is not higher than 0,5–1% of GSH [4, 48].

Oxidized glutathione (GSSG) can be reconverted into two molecules of reduced GSH by the enzyme glutathione reductase and NADP-H: $GSSG + NADP\text{-}H + H_2 \rightarrow 2GSH + NADP\text{-}H_2$.

The most reactive group in the glutathione molecule is a sulfhydryl group of cysteine residue –SH, which easily enters into reactions of one- and two-electron oxidation, thiol-disulfide exchange, alkylation and acetylation, providing numerous functions of glutathione in the cell [4, 42].

Being a powerful antioxidant, glutathione interacts directly with free radicals, superoxide, singlet oxygen, and hydroxyl radicals [7, 13].

Glutathione also performs its antioxidant function as a coenzyme of glutathione peroxidase. This enzyme is known to catalyze the reduction of hydrogen peroxide and hydroperoxides to water or alcohol ROH. It should be noted that currently 7 isoforms of glutathione peroxidases are known [4], the function of which is not limited to the antioxidant effect. For example, the 4th isoform is involved in the inhibition of inflammatory processes by influencing lipoxygenases and cyclooxygenases [66]. The glutathione peroxidase deficiency, which is directly associated with a decrease in glutathione concentration, contributes to the development of acute and chronic inflammation of the cardiovascular system and intestines, accelerates the formation of atherosclerosis, and increases embryonic mortality [42].

In the glutathione-ascorbate-tocopherol chain, which is part of the body's antioxidant defense system, glutathione plays a key role, carrying out the reduction of oxidized ascorbic acid and tocopherol [47].

It is important to remember that for the normal functioning of the body, a small amount of reactive oxygen species is necessary, which are involved in the transmission of signals in cells [31]. This is why introducing excess amounts of glutathione into the body can lead to adverse effects.

Glutathione is associated with energy metabolism in the cell. Its level is critical for optimal and efficient oxidation of mitochondrial fatty acids. With insufficient glutathione levels, oxidation of non-esterified fatty acids in mitochondria is reduced, which has been demonstrated in both animals and humans [51]. Correction of glutathione deficiency results in restoration of impaired mitochondrial fatty acid oxidation.

In the process of nutrient oxidation in mitochondria, reactive oxygen species are formed, which can damage the mitochondria. GSH deficiency results in mitochondrial dysfunction, which can be corrected by correcting glutathione levels [40].

Glutathione transferases play a major role in the metabolism of endogenous and exogenous xenobiotics, catalyzing reactions of conjugation, reduction, isomerization, etc. [48]. Numerous glutathione transferases are grouped into three families: cytosolic, mitochondrial, and microsomal. Some of them are involved in the synthesis of prostaglandins and leukotrienes, testosterone and progesterone, and tyrosine degradation [4].

Detoxification processes occur in all cells, and are especially active in the liver, where electrophilic xenobiotics of almost all classes are neutralized. These xenobiotics include a variety of substances: pesticides, drugs, smoking products, paints, carcinogens and mutagens. The addition of glutathione helps reduce toxicity by decreasing their activity and leads to a more rapid elimination of these compounds from the body, as their hydrophilicity increases.

As early as the 1980s, it was believed that detoxification of exogenous xenobiotics was the main function of glutathione transferases. Nowadays, it is clear that the primary function of glutathione transferases is to participate in the metabolism of toxic endogenous substances. Already in prokaryotes, glutathione transferases perform the conjugation of GSH with secondary metabolites of oxidative stress — aldehydes, quinones, epoxides [42].

Glutathione plays a key role in many forms of programmed cell death, including apoptosis, necroptosis, ferroptosis and autophagy [8, 25, 30, 55]. Apoptosis is initiated and triggered by the caspase family. A decrease in GSH/GSSG ratio in the cell precedes the activation of caspases and is considered an early event in the progression of apoptosis in response to various stimuli [28, 35]. In some cases, GSH depletion not only triggers one form of programmed cell death, but can also initiate multiple forms of cell death. These different forms of cell death can be initiated simultaneously or sequentially and then interact with each other [23, 27, 68].

Glutathione is directly involved in cell proliferation. Thus, when there is insufficient GSH content in the nucleus, the cell cycle stops at the G1 phase. At the onset of cell proliferation, GSH creates the necessary redox environment to stimulate chromatin degradation. Nuclear glutathione is required to control nuclear protein degradation by the nuclear proteasome [2, 30, 55].

The normal course of innate and acquired immunity processes cannot occur without GSH. Immune cells use active forms of oxygen to eliminate pathogens. Glutathione is used to contain this process within the infectious focus and prevent excessive impact on surrounding tissues. In addition, it is important for the regulation of such processes as proliferation of T-lymphocytes, the phagocytic activity of polymorphonuclear neutrophils, and the functions of dendritic cells [41, 54, 64, 65].

Glutathione is essential for cells to repair damaged areas of DNA, proteins and other biomolecules. Synthesis and repair of damaged DNA occurs with the participation of the enzyme ribonucleotide reductase (RNR). The GSH-glutathione reductase system is an electron donor for this enzyme, thereby supporting DNA synthesis and repair [30, 62].

Glutathione is the first protective barrier for the lens, cornea, retina, skin, lungs and intestinal mucosa [46, 50].

Thus, glutathione status is an indicator of cell viability. When the glutathione system is depleted, the functionality and resistance of cells decreases sharply, even to the point of death.

FACTORS THAT DEPLETE THE GLUTATHIONE SYSTEM

Various exogenous and endogenous factors of physical or chemical etiology can deplete the glutathione system. Viral infections [36], various radiations [52], including ultraviolet [24], toxins including alcohol, heavy metals, inflammation, household chemicals and dietary deficiency of glutathione and its precursors lead to a decrease in the concentration of reduced glutathione [6, 43].

With aging, the level of reduced glutathione decreases, and the oxidized one increases [42, 59, 67]. This deterioration of GSH homeostasis may participate, along with other physiological phenomena, in the development of age-related diseases.

Thus, oxidative depletion of glutathione can outpace its synthesis. In such situations, the body is extremely important to be able to obtain glutathione from exogenous sources. Naturally, questions arise about the presence and

quantity of glutathione in food, the possibility of transporting this substance from the gastrointestinal tract to blood plasma and its interorgan transport.

GLUTATHIONE CONTENT IN FOOD

Glutathione is a common component of human nutrition, as it is part of all animal cells, yeast and many plants [4, 7, 42, 49]. Human nutritional sources contain both reduced and oxidized glutathione. The total content of glutathione (GSH+GSSG) in 100 g of fresh liver is about 200 mg, in 100 g of meat is about 50 mg, in plant products its content ranges from 1 to 28 mg per 100 g of product [1, 6].

L. Pilat et al. (2012) provide lists of products that contain not only glutathione, but also its inactivating substances (GRU). The authors also indicate products that contain only glutathione, or only its inactivators, or both [6].

For example, in the list of products containing only glutathione (GSH+GSSG), boiled asparagus is in first place (916 nmol/g total GSH). This list also includes meat products, including veal chop and fried beefsteak — 774 and 434 nmol/g, respectively, vegetables (cauliflower, broccoli, tomatoes, carrots, cucumbers, etc.) — an average of 200 nmol/g, fruits (oranges, peaches) — 237 and 241 nmol/g, etc. In the list of products containing only GRU (where GRU was defined as the amount of GSH reacting with a food sample, nmol/g food), milk and some dairy products are in the first place, followed by cherries, blueberries, prunes, and among drinks, the most important are tea, coffee, etc. There is a fairly extensive list of products containing glutathione and substances that inactivate it. The authors note that fresh fruits and vegetables generally contain more glutathione than GRU, although the amount of glutathione varies widely. Cereals such as corn and fortified white bread contained GRU and very little GSH, while rice, oatmeal, and whole white bread had relatively high levels of GSH and low levels of GRU.

GLUTATHIONE TRANSPORT

How is glutathione transported from food into the body's internal environment? It is known that intestinal epithelial cells have a special transporter for glutathione and are able to import it from the intestinal lumen in an intact form [42, 66]. In parallel to this process, enterocytes, using the enzymes gamma-glutamyl transferase and dipeptidase, hydrolyze glutathione into amino acids. Then, these amino acids are transported into the cell, where glutathione is synthesized again.

For intracellular transport of glutathione through internal membranes, dicarboxylate and oxoglutarate transporters are used [53]. Interorgan transport of glutathione is carried out with the help of three groups of proteins: multidrug resistance proteins, polypeptides that transport organic anions, and Ral-binding proteins [15, 16]. Glutathione, which is synthesized in hepatocytes, is transported into blood plasma, epithelial lining fluids and exocrine secretions (e.g. bile, unchanged, without degradation) [10, 15, 17]. In rat liver, approximately half of GSH is released into plasma and half passes through the tubular membrane into bile [16].

CHANGES IN GLUTATHIONE CONTENT IN THE BODY DEPENDING ON TYPE OF ADMINISTRATION

The effectiveness of glutathione in dietary supplements is highly controversial. Thus, animals have demonstrated good results from the use of glutathione, which were accompanied by an anticarcinogenic effect [60], an improvement in the immune status [29], and an increase in the detoxification function [38].

At the same time, the effectiveness of oral glutathione in humans is controversial. Researchers associate this with the amount and activity of the intestinal enzyme γ-glutamyl transpeptidase, which breaks down glutathione [9, 69].

However, there is a six-month randomized, double-blind, placebo-controlled study that showed that oral glutathione supplementation at 250 or 1000 mg/day resulted in significant increases in body glutathione stores in 54 non-smoking adults [58]. At the same time, good results have been shown using sublingual glutathione [22, 61]. The authors demonstrated that with a sublingual dosage form, the tripeptide GSH is directly assimilated through the buccal mucosa. Sublingual administration of glutathione (450 mg/day) resulted in an increase in plasma GSH. In addition, a secondary effect of glutathione administration was a significant increase in plasma vitamin E.

Based on the above studies, it can be assumed that dietary glutathione is partly absorbed through the oral mucosa, and partly through the gastrointestinal tract. Part of it is hydrolyzed by the intestinal and liver enzyme γ-glutamyl transpeptidase.

EFFECT OF DIFFERENT DIETS ON GLUTATHIONE HOMEOSTASIS

The Mediterranean diet, which is characterized by high consumption of vegetables, fruits, greens, extra virgin olive oil, cereals, legumes, nuts, moderate consumption of red wine, fish, dairy products, showed an inverse relationship with the level of GSSG and, accordingly, with an increase in the GSH/GSSG ratio, regardless of family and genetic factors [26]. In another study, adherence to the Mediterranean

diet in adult men and women showed a positive association with GSH levels and an inverse association with GSSG [18]. Calculations were made after adjustment for age, body mass index, sex, race, and history of chronic diseases.

The DASH diet, which was developed for the treatment and prevention of hypertension, promotes an increase in plasma GSH levels [11, 12, 57]. This diet includes 5 servings of fresh vegetables and fruits per day, 7 servings of carbohydrates (whole grains, legumes), 2 servings of meat and 2 of dairy products, nuts and seeds — 2–3 servings per week. The diet emphasizes reduced intake of saturated fat and sodium.

Analysis of the effects of vegetarian diets has shown conflicting results: a number of studies have recorded an increase in GSH in blood plasma, mainly in individuals with chronic diseases and reduced baseline glutathione levels [34, 63], while other studies, on the contrary, have demonstrated its decrease [39] or no changes there [33, 37, 56]. Such mixed results of vegetarian diets are most likely related to possible amino acid deficiency that disrupts GSH synthesis.

Diets typical of modern urban populations and containing insufficient amounts of fresh vegetables and fruits may be associated with decreased plasma GSH levels [45].

CONCLUSION

Optimal functioning of the glutathione system in the body is directly related to health reserves, prevention of many diseases, slowing down the aging process and increasing life expectancy. Maintaining normal glutathione levels is possible with dietary optimization, especially in cases where the body's antioxidant systems are depleted under the influence of unfavorable factors. Studies are needed to examine the effects of including glutathione-containing foods in the diet and, conversely, excluding glutathione-depleting foods from the diet during oxidative stress and other adverse effects on the body.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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PATHOPHYSIOLOGY OF HEMOSTASIS (LECTURE)

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Abstract. The mechanisms of development of many very common diseases (myocardial infarction, stroke, tumors, infectious pathology, and others) are associated with pathological changes in the hemostasis system. Understanding the pathophysiology of these changes is at the heart of proper diagnosis and effective treatment. This lecture, intended for medical students and doctors of various specialties, briefly summarizes the basic ideas about the structural components and mechanisms of the hemostasis system, presents the main groups of hemostasiopathies, describes the types, causes and mechanisms of the development of hemorrhagic diathesis, thrombophilic syndromes, thrombohemorrhagic syndrome.

Keywords: hemostasis, hemorrhagic syndrome, thrombophilic syndrome, thrombohemorrhagic syndrome

ПАТОФИЗИОЛОГИЯ СИСТЕМЫ ГЕМОСТАЗА (ЛЕКЦИЯ)

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Резюме. Механизмы развития многих весьма распространенных заболеваний (инфаркт миокарда, инсульт, опухоли, инфекционная патология и др.) связаны с патологическими изменениями в системе гемостаза. Понимание патофизиологии этих нарушений лежит в основе правильной диагностики и эффективного лечения. В данной лекции, предназначенной для студентов медицинских вузов и врачей различных специальностей, кратко изложены базовые представления о структурных компонентах и механизмах функционирования системы гемостаза, представлены основные группы гемостазопатий, описаны виды, причины и механизмы развития геморрагических диатезов, тромбофилических синдромов, тромбогеморрагического синдрома.

Ключевые слова: гемостаз, геморрагический синдром, тромбофилический синдром, тромбогеморрагический синдром

Hemostasis pathology plays an important role in mechanisms of development of many common diseases, including those that are the most common causes of death worldwide, such as coronary heart disease (CHD), stroke, diabetes mellitus, tumors, infectious diseases, injuries, obstetric and gynecological pathology, autoimmune diseases, hemorrhagic diathesis, etc. All types of shock also inevitably cause disturbances in hemostatic system. Thromboembolic complications, one of the severe consequences of hemostasopathies, are the direct causes of death in 25% of fatal

outcomes worldwide [30, 31]. The prevalence and significance of hemostasopathies creates the need to develop in medical students and doctors of various clinical specialties correct, based on modern scientific data, basic knowledge about structural components, functions, possible pathologies of hemostasis, the causes and mechanisms of their development and consequences.

BRIEF DESCRIPTION OF HEMOSTASIS PHYSIOLOGY

It is possible to understand the pathology of hemostasis only on the basis of knowledge about its normal physiology. According to modern concepts, the hemostatic system is a set of structural components (so-called links) and finely balanced, partially antagonistic mechanisms that ensure the cessation of bleeding when the vascular wall is damaged, the local and reversible nature of thrombosis and the liquid state of blood and the integrity of blood vessels outside the damage [17, 18, 22, 23, 40]. By ensuring blood fluidity and integrity of bloodstream, regulating the aggregate state of blood [14], the hemostatic system forms dynamic space of internal environment of the body, largely determining homeostasis. When the vascular wall is damaged, blood composition changes, or the nature of blood flow is disrupted (the classic Virchow triad, which determines the conditions for thrombus formation), thrombus formation mechanisms are activated in the hemostatic system, aimed at stopping bleeding and localizing the pathological process. These mechanisms ensure the formation of a barrier around the site of inflammation, and also participate in non-specific defense reactions and in the mechanisms of restoration of damaged tissue. Insufficiency or excess of these mechanisms in pathological conditions can lead to the development of hemorrhagic and thrombophilic syndromes, respectively.

The main structural components of the hemostatic system are three links: vascular, cellular and plasma. All three links interact closely with each other, ensuring a balance between the mechanisms of thromboresistance and the processes of thrombus formation. In the vascular link, the key role is played by endothelial cells, lining the bloodstream from the inside and representing, due to the wide range of biologically active substances synthesized by them, a giant endocrine, paracrine and autocrine organ of the human body. Such an organ regulates the activity of platelets and leukocytes, tone and permeability of blood vessels, and activity of coagulation, anticoagulation and fibrinolytic systems [2, 18]. Physiologically, intact endothelium provides so-called thromboresistance by producing antiplatelet agents — NO, PgI_2 (prostacyclin), ERF (endothelial relaxing factor); anticoagulants — glycosaminoglycans (heparan sulfate, dermatan sulfate, etc.), thrombomodulin, TFPI (tissue factor pathway inhibitor); fibrinolysis activators — t-PA (tissue plasminogen activator) and u-PA (urokinase plasminogen activator). When the vascular wall is damaged by exogenous and endogenous factors, it reacts with immediate spasm and turns into a powerful thrombogenic surface that activates platelets and coagulation cascade. The damaged endothelium begins to produce vasoconstrictors — endothelin-1; aggregators — PAF (platelet activating factor); VWF (von Willebrand factor) — an adapter of platelet adhesion to subendothelial collagen exposed as a result of damage; TF (tissue factor), which triggers coagulation cascade (produced primarily by subendothelial smooth muscle cells and fibroblasts); TFPI-1 and TFPI-2 (tissue plasminogen activator inhibitors), limiting fibrinolytic activity at the site of hemostatic plug formation [1, 10, 11, 40].

Platelets are a key component of cellular link of hemostasis. They are the smallest, with a diameter of about 3 μm, anuclear cellular elements of blood, formed during fragmentation of megakaryocytes localized in bone marrow and, as has been shown in modern studies, in microvessels of lungs [19, 20, 29]. The number of platelets in peripheral blood ranges from 180 to 400×10^9 per liter. The lifespan of platelets in the bloodstream is 7–10 days. Despite the absence of a nucleus and small size, the structure of platelets is very complex and surprisingly flexible. These are quite consistent with their diverse functions, which include not only hemostatic, but also trophic (primarily in relation to the vascular wall), participation in immune reactions, angiogenesis and regeneration [7, 19, 20, 25, 29, 32].

On the surface of platelets there is a wide range of receptors, the entire spectrum of which cannot be characterized within the framework of this lecture. Some of these receptors are expressed and activated when the vascular wall is damaged and cause adhesion and aggregation, that is, platelets sticking to the site of damage to the vascular wall and sticking together, respectively. Of particular importance among these receptors, in light of the subsequent discussion of hemostatic defects, is transmembrane receptor complex GPIb-V-IX. On average, 25,000 such complexes are present on the platelet membrane. The complex interacts with a von Willebrand factor. This factor acts as an adapter of platelet adhesion to subendothelial collagen exposed as a result of damage. Also it is involved in activation of platelets and their interaction with coagulation factors FXI, FXII, high-molecular-weight kininogen (HMWK), and FVIIa. The role of glycoprotein receptor GPVI is also important, causing direct interaction of platelets with collagen (without intermediaries) at later stages of adhesion. In mechanisms of platelet aggregation, the key role is played by integrin receptors GPIIb/IIIa ($\alpha_{II}b\beta_{III}$). These receptors are present on the

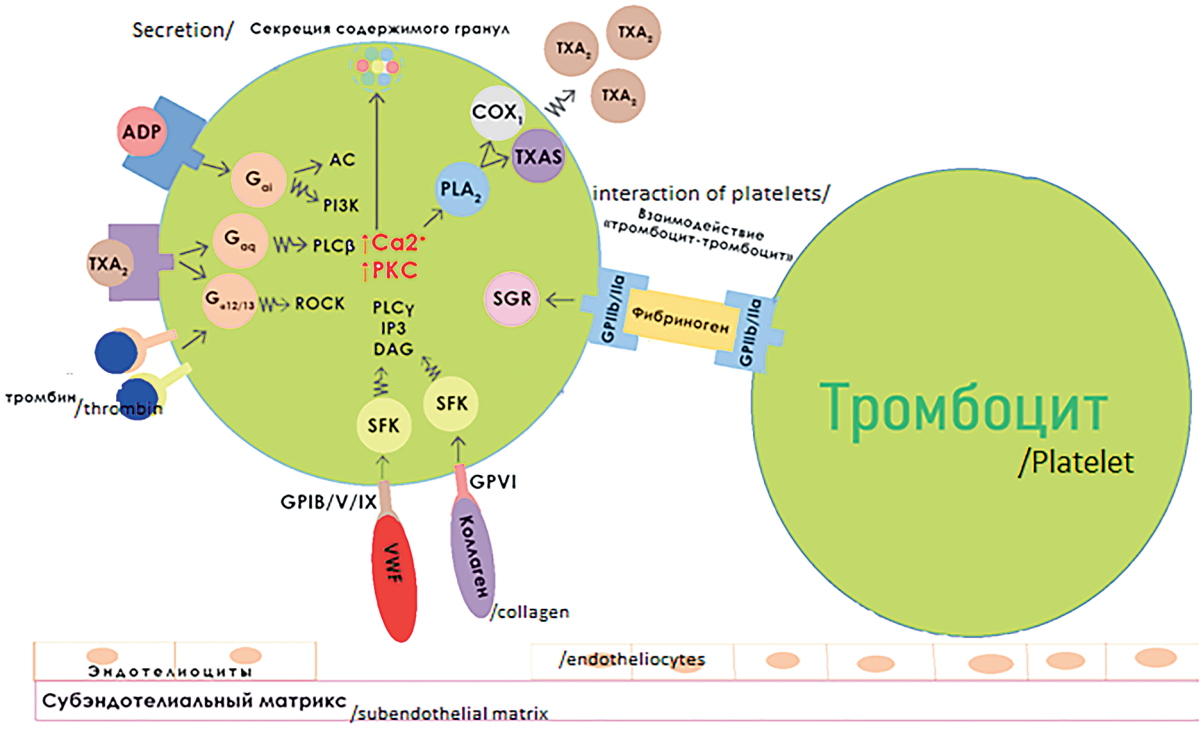

Fig. 1. Mechanisms of platelet involvement in primary hemostasis [12]

Примечания/notes: ADP — аденозиндифосфат/adenosine diphosphate; TXA2 — тромбоксан А2/thromboxane A2; Gai — α-субъединица G-белка/the G-protein subunit; Gaq — αq-субъединица G-белка/the G-protein subunit; Gα12/13 — α12/13-субъединицы G-белка/the G-protein subunits; AC — аденилатциклаза/adenylate cyclase; PI3K — фосфоинозитид-3-киназа/phosphoinositide 3-kinase; PLCβ — фосфолипаза Cβ/phospholipase Cβ; PLCγ — фосфолипаза C γ/phospholipase C γ; PLA2 — фосфолипаза А2/ phospholipase A2; ROCK — Rho-ассоциированная протеинкиназа/Rho-associated protein kinase; IP3 — инозитол-3-фосфат/inositol-3-phosphate; DAG — диацилглицерол/diacylglycerol; SFK — Src семейство киназ/Src family kinases; GP (IB, IIa, IIb V, VI, IX) — гликопротеины/glycoproteins; VWF — фактор фон Виллебранда/the von Willebrand factor; SGR — малый регулятор G-белка/small G-protein regulator; COX1 — циклооксигеназа 1/cyclooxygenase 1; TXAS — тромбоксан А2-синтаза/thromboxane A2 synthase

Рис. 1. Механизмы участия тромбоцитов в первичном гемостазе [12]

surface of platelets in the greatest numbers. On average, there are about 80,000 receptors per platelet, with about 40,000 copies stored in the α-granules and in the open canalicular system. In the absence of vascular wall damage, they are located on platelet membranes in an inactive conformation. They can be activated by collagen, podoplanin, thrombin, thromboxane A_2, ADP, and epinephrine. In an active open conformation, they interact with bivalent ligands: fibrinogen, VWF, fibronectin, vitronectin, which bind platelets to each other [29, 32] (Fig. 1).

Platelets contain three types of granules in cytoplasm: α-granules, dense granules, and lysosomal granules. Their total number is about 70 per platelet. α-Granules are the most numerous (50–60 per platelet) and largest. These granules contain about 300 different proteins involved in coagulation, adhesion and aggregation of platelets, acting as receptors and growth factors, in particular fibrinogen, FV, P-selectin, platelet-derived growth factor, etc. Dense granules contain smaller molecules: ADP, ATP, serotonin, calcium. Hydrolytic enzymes are present in lysosomal granules [19, 20].

At rest, in the absence of effects that threaten homeostasis, platelets have a disc-shaped form. They are pushed by axial blood flow, represented by erythrocytes, to endothelium, where platelets perform a trophic function, participate in microcoagulation, maintaining thromboresistance. However, when damage occurs, platelets not only adhere to the site of vascular wall defect, but they are also activated. This is accompanied by a change in shape from discoid to process-like. A reaction of platelet release occurs in the form of secretion of granules content through an open canalicular system into blood and onto the platelet membrane. This enhances both platelet aggregation and activation and coagulation cascade by the positive feedback mechanism. The production of thromboxane A_2 (TxA_2) in platelets, an important stimulator of aggregation, also increases. The conformation of receptors changes. Phosphatidylserine is transferred from the inner bilayer of phospholipid membrane to the outer one, which causes a procoagulant surface formation on platelet membrane [16, 29, 39] (Fig. 1).

In addition to platelets, other blood cells also play a significant role in hemostasis. In particular, neutrophils participate

in thrombus formation by interacting with platelet aggregates via P-selectin receptors on the platelet surface. Neutrophils adhere to damaged endothelium and are capable of releasing nuclear chromatin into extracellular space, forming so-called neutrophil extracellular traps (NETs), which activate coagulation. In 2004, this interesting phenomenon was discovered by Brinkman et al. and named NETosis [34].

Erythrocytes are also important participants in the cellular link of hemostasis, largely determining hemorheological properties of blood. They can form aggregates with platelets, participating in the formation of red thrombi, releasing ADP and TxA_2, which stimulate platelet adhesion and aggregation, and suppressing fibrinolysis activity [41]. Mechanisms of participation of cellular and vascular links in stopping bleeding are conventionally called primary (vascular-platelet) hemostasis.

The plasma link of hemostasis includes components of coagulation, anticoagulation and fibrinolysis. Components of the coagulation system are represented by so-called coagulation factors: serine proteases that cascade-activate each other, and their cofactors. Since the work of Morawitz (1905), a number of key stages have been identified in coagulation process: the release of tissue factor (in past terminology, tissue thromboplastin), conversion of prothrombin (fII) by activated thromboplastin into thrombin (fII_a) in the presence of calcium, and the conversion of fibrinogen (fI) into fibrin (fI_a) under the action of thrombin. Formed in the 1960s the cascade model of coagulation characterizes stages of this process in more detail and distinguishes between the so-called internal, all components of which are present in the bloodstream, and external, which is activated by TF coming from outside, pathways for the formation of prothrombinase complex (Fig. 2). This model is quite suitable for describing the process of blood clotting *in vitro*, in particular during laboratory tests such as PT (prothrombin

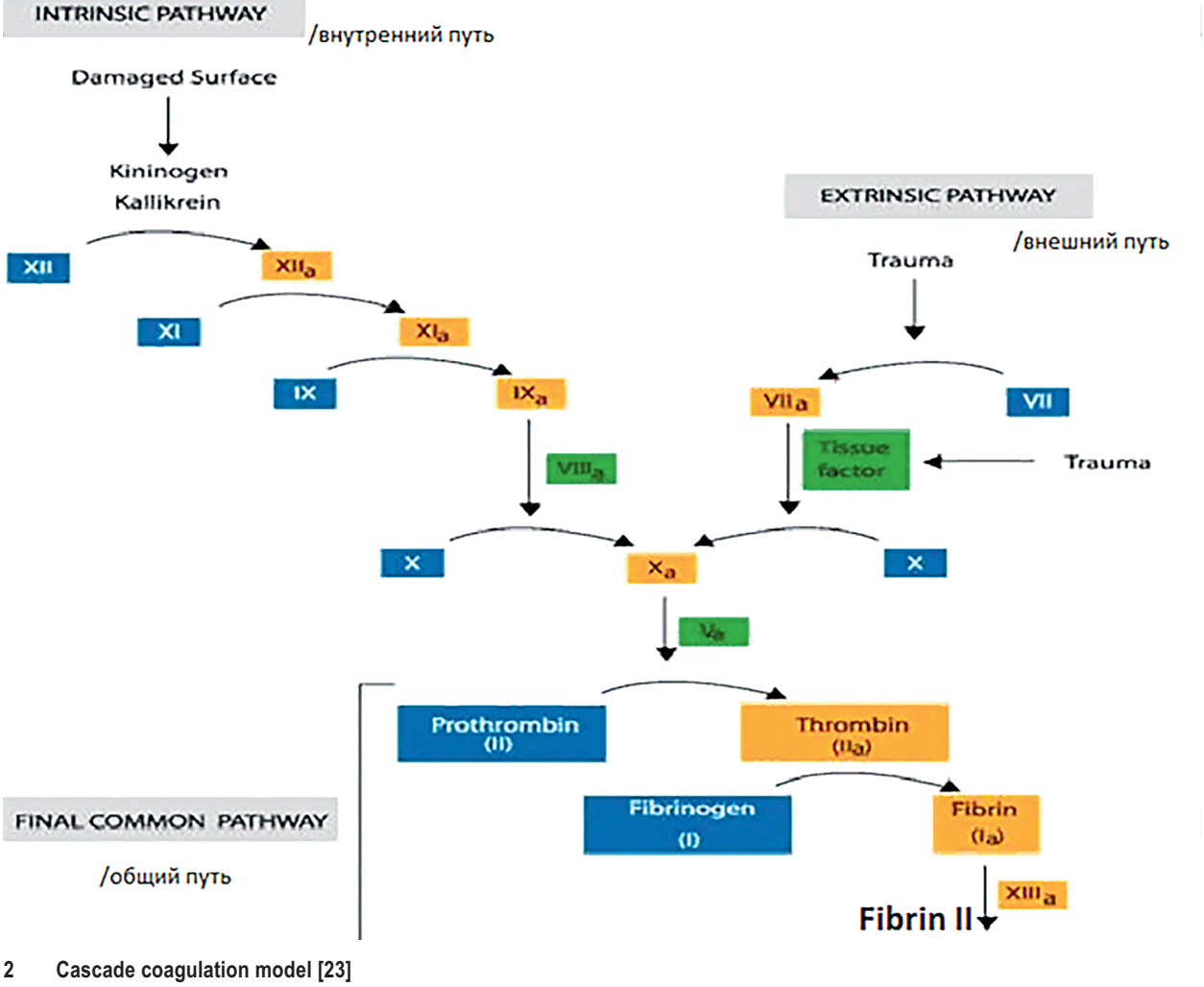

Fig. 2 Cascade coagulation model [23]
Рис. 2. Каскадная модель коагуляции [23]

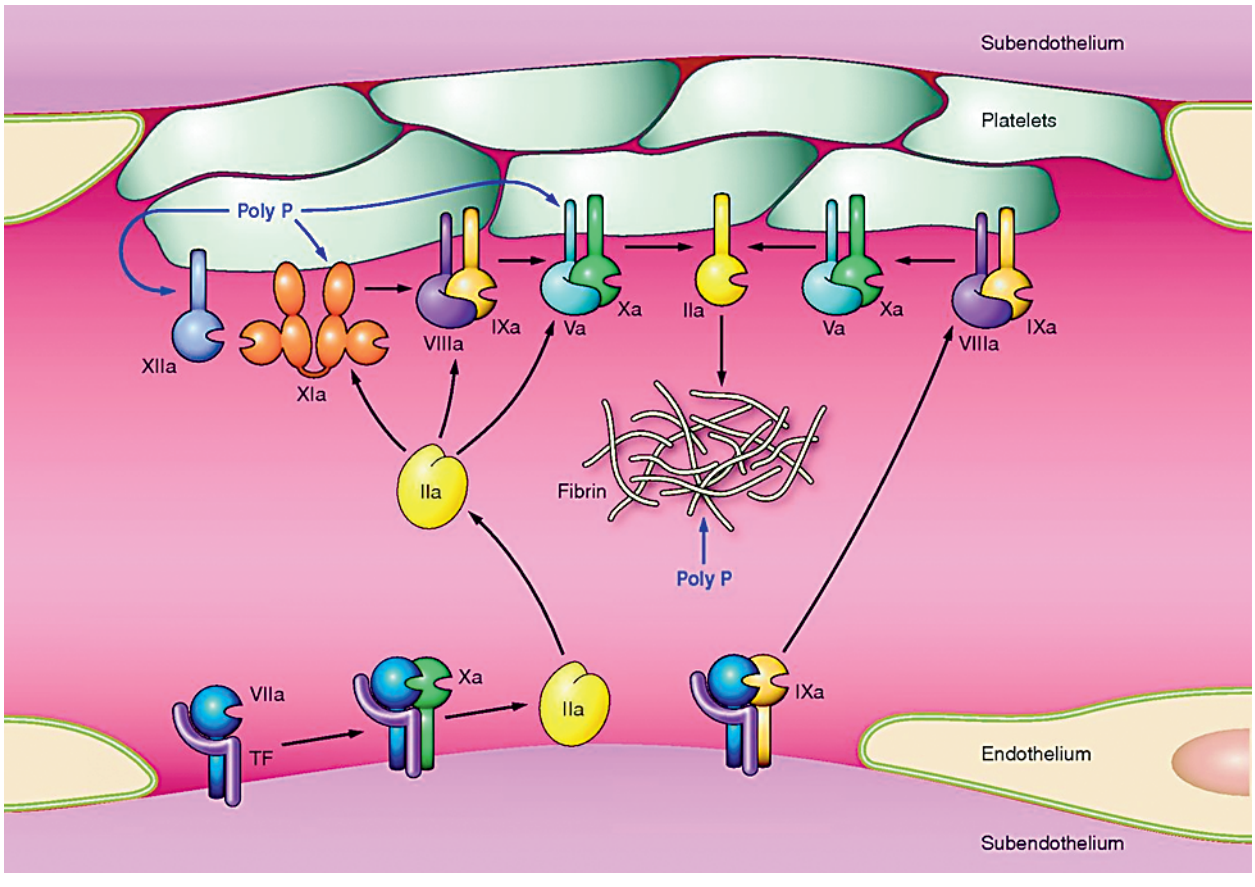

Fig. 3. Cellular model of coagulation (figure taken from [40])
Рис. 3. Клеточная модель коагуляции (рисунок взят из [40]). TF — тканевой фактор; IIa — тромбин; Poly P — полифосфаты; Platelets — тромбоциты; Subendothelium — субэндотелий; Endotyelium — эндотелий

time) and APTT (activated partial thromboplastin time), and is therefore still relevant.

However, in the XXI century, ideas about mechanisms of blood coagulation *in vivo* have undergone serious revision, and a cell biological model of coagulation has been formed [21, 33, 38]. This model distinguishes three stages: initiation, amplification, and propagation. During initiation, smooth muscle cells and fibroblasts exposed as a result of damage to the vascular wall endothelium express tissue factor, which binds to factor VII and activates it. The TF/VIIa complex proteolytically activates small amounts of factors IX and X. FXa binds to FVa on the surface of TF-expressing cells to form a prothrombinase complex, which converts prothrombin to thrombin. During the amplification stage, a small amount of thrombin formed in the previous phase activates platelets adhered to the site of vascular wall damage, and also activates FV, FVIII, and FXI. This closes the positive feedback loop, i.e., enhances thrombin formation. The propagation stage occurs on a procoagulant surface of activated platelets, rich in phosphatidylserine. Activated FXI activates FIX, which then activates FVIII on the platelet surface, forming the fIXa/fVIIIa tenase complex, which catalyzes formation of fXa. The prothrombinase complex fXa/fVa then converts prothrombin to thrombin, which in turn catalyzes fibrin formation. In parallel, polyphosphates (Poly P) released by activated platelets can further stimulate activation of factor XII, factor V, and factor XI and inhibit thrombus lysis (Fig. 3).

According to the cell biological model, the so-called intrinsic pathway serves to amplify extrinsic pathways. Three physiological triggers of intrinsic pathway have been identified, namely collagen, linear phosphate polymers (polyphosphates), and neutrophil extracellular traps (NETs) [40]. The involvement of the coagulation system in stopping bleeding is conventionally called secondary coagulation hemostasis.

Coagulation is restrained by the anticoagulation system. It is represented by a whole set of protease inhibitor proteins found in plasma and causing a limited, localized nature of thrombus formation. These primarily include antithrombin, heparin cofactor II, tissue factor pathway inhibitor (TFPI), C1 inhibitor, proteins C and S. Interestingly, thrombomodulin plays an important role in protein C activation.

It is a transmembrane protein found on endothelial cells. Thrombomodulin forms a complex with thrombin, which activates protein C bound to a corresponding receptor on endothelium. Thus, thrombin is used in this case as an activator of one of the important components of the anticoagulant system [40].

The reversibility of thrombosis is ensured by the fibrinolytic system. The key component of this system is plasmin (fibrinolysin), formed from plasminogen. The conversion of plasminogen to plasmin is catalyzed by plasminogen activators, among which the greatest importance is given to tissue plasminogen activators (t-PA, u-PA) produced by endothelium, monocytes, and megakaryocytes. Plasmin breaks down fibrin and fibrinogen. As a result, FDPs (fibrin and fibrinogen degradation products) are formed, some of which have properties of secondary anticoagulants and antithrombotics. For example, fragment Y competitively inhibits thrombin, fragments D and E inhibit platelet aggregation. Plasmin is also capable of breaking down a number of coagulation factors: V, VIII, XI, XII, XIII, FV. The process of plasmin formation is balanced by a number of inhibitors. These include plasminogen activator inhibitors (PAI-1, PAI-2, PAI-3), formed in endothelium, smooth muscle cells, platelets, and inhibitors of plasmin itself, the most important of which is α_2-antiplasmin, produced by the liver [23].

PATHOGENESIS OF HEMOSTASOPATHIES. GENERAL CONCEPTS. MAIN GROUPS OF HEMOSTASOPATHIES

Hemostatic system, thanks to the mechanisms of checks and balances under physiological conditions, a dynamic balance is maintained between mechanisms involved in stopping bleeding (primary and secondary hemostasis) and mechanisms causing thromboresistance (let's call them antihemostasis). Violation of this balance is the basis of hemostasopathies. In principle, three variants of imbalance in the hemostatic system can be distinguished. The first variant is represented by conditions in which the mechanisms of stopping bleeding for various reasons are insufficient in relation to the mechanisms of thromboresistance. The result of such imbalance is a tendency to increased bleeding (hemorrhagic diathesis — group I of hemostasopathies). The second variant is represented by a large group of hereditary and acquired disorders, in which mechanisms of thrombus formation prevail over mechanisms of thrombus resistance. Such conditions, characterized by an increased tendency to thrombus formation, are called thrombophilic syndromes. If the hemostatic system was static, then variants of hemostasopathies would be limited to this. However, in a dynamic system, a third variant of imbalance is possible, a kind of "swing". In this case, in the first phase, the balance is pathologically shifted towards mechanisms of thrombus formation with excessive uncontrolled generalized thrombus formation in vessels of various areas. During the second phase, a shift in the balance in the opposite direction is observed with the development of pathological deficiency of platelets and coagulation factors as a result of their excessive consumption. Because of this, a patient experiences increased bleeding (Fig. 3). The general name for group III of hemostasopathies is thrombohemorrhagic syndrome. The most common example of this variant is DIC — disseminated intravascular coagulation syndrome.

Let's take a closer look at each of the above three main groups of hemostasis.

BRIEF GENERAL CHARACTERISTICS OF HEMORRHAGIC DIATHESIS

Hemorrhagic diathesis is characterized by an increased tendency to bleeding and can develop as a result of pathological defects in various parts of the hemostasis system: vascular, cellular and plasma. Hemorrhagic diathesis caused by defects of the vascular link is called vasopathy, of the cellular link — thrombocytopathy and thrombocytopenia, of the plasma link — coagulopathy. According to etiology, the three above-mentioned types of hemorrhagic diathesis can be hereditary and acquired. It is impossible to describe in detail the causes and mechanisms of all diseases characterized by increased bleeding in one lecture. It remains possible to characterize some of the most relevant mechanisms of damage to blood vessels, platelets, and the coagulation system.

Among mechanisms that damage the vascular wall and underlie hemorrhagic vasculitis, immunopathological ones are common. As a result of provoking factors' actions (bacterial, viral, drug antigens) immune complexes are formed in predisposed patients, deposited in skin microvessels, kidneys, gastrointestinal tract and other areas. Immune complexes are capable of activating the complement system and causing inflammation of the vascular wall with the development of bleeding. These mechanisms are the basis of Henoch–Schönlein purpura (infectious-allergic capillary toxicosis), which is very common in children and clinically manifests as purpura in the form of diffuse, fine-point, hemorrhagic rash. Along with skin vessels, microvasculature of kidneys, gastrointestinal tract, and periarticular areas can be affected [28].

In addition to immunopathological mechanisms, a number of other factors can also lead to vascular wall damage: increased blood pressure, metabolic disorders, direct damaging effects of toxins, infectious agents, drugs, vitamin deficiency, in particular vitamin C deficiency (scurvy). Vitamin C

is necessary for the post-translational modification of collagen (hydroxylation of proline and lysine). Collagen plays an important role in the interaction of platelets with the vascular wall during so-called vascular-platelet hemostasis. Collagen defect leads to increased bleeding.

Hereditary collagen defects in Ehlers-Danlos syndrome and Marfan syndrome may also be accompanied by bleeding tendency. The most common hereditary vasopathy accompanied by hemorrhagic syndrome is Rendu–Osler–Weber disease (hereditary hemorrhagic telangiectasia) [23, 27]. In the vast majority of cases, the disease is based on a defect in genes located on chromosomes 9 and 12, encoding endothelial membrane glycoprotein endoglin (type 1) and ACVR1 protein (formerly ALK-1) (type 2), which are involved in interaction with TGFβ (transforming growth factor β). As a result, patients experience vascular wall defects with dilation of capillaries and venules, formation of telangiectasias, arteriovenous shunts, and a high risk of vascular wall rupture and bleeding. Most patients (90% of cases) experience nosebleeds from pathologically dilated defective vessels of nasal mucosa. In addition, vessels of skin (75%), lungs (33–50%), liver (30%), gastrointestinal tract (15%), and the central nervous system (5–23%) may be affected [24].

Deficiency in the quantity (thrombocytopenia) and defects in the quality (thrombocytopathy) of platelets underlie most hemorrhagic diathesis (up to 80%, according to Barkagan Z.S.) [3]. Fundamentally, thrombocytopenia can result from increased destruction of platelets and/or their precursors — megakaryocytes, increased consumption of platelets during thrombus formation, decreased production of platelets in bone marrow (for example, in aplastic anemia), blood loss, sequestration of platelets in spleen [23].

The most common are destructive thrombocytopenias caused by immunopathological mechanisms. In adults, the most typical form of immunopathological thrombocytopenia is Werlhof's disease (chronic immune thrombocytopenic purpura), which most often affects women aged 20–30. In essence, Werlhof's disease is an autoimmune disease, when, for reasons not entirely clear, antibodies to normal antigens on the surface of platelets, in particular to GPIIb/IIIa aggregation receptors, are formed. Platelets labeled with antibodies are eliminated in spleen, severe thrombocytopenia (less than $10–20\times10_9$/l) occurs, accompanied by nasal and gastrointestinal bleeding, menorrhagia, petechiae, and ecchymosis on skin.

Immune thrombocytopenia is also common in children, often occurring after viral infections (rubella, chicken pox, influenza), vaccination, or taking medications (quinine, quinidine, drugs with gold content, heparin). Unlike Werlhof's disease, in this case the body of a sick child produces antibodies against viral and other heteroantigens adsorbed on the surface of platelets. Since viral antigens are eliminated over time, immune thrombocytopenic purpura in children in 80% of cases passes spontaneously within 2 months [23]. Immune thrombocytopenia can also occur in utero in a child with antigenic incompatibility of maternal and fetal platelets (isoimmune variant) or a mother with Werlhof's disease (transimmune variant).

Important mechanisms of thrombocytopathies are hereditary defects of various structural components involved in platelet hemostasis. Considering the complexity of the structure of platelets, a fairly wide variety of hereditary defects is observed. The most common hereditary disease leading to a disorder of not only platelet but also coagulation hemostasis is von Willebrand disease. This disease is based on defects in a gene located in chromosome 12 and encoding VWF. VWF is synthesized in endothelium and megakaryocytes, has a complex multimeric structure and is involved in processes of initial adhesion of platelets to subendothelial collagen, playing the role of an adapter and interacting, on the one hand, with collagen, on the other hand, with GPIb-V-IX receptors on the platelet surface. In addition, VWF binds to circulating factor VIII, stabilizing it and localizing it at the site of activation of bleeding arrest mechanisms. In different forms of von Willebrand disease, a decrease in the total amount of VWF (occurs in 70%) or qualitative defects of various VWF domains are possible, causing various ratios of platelet and coagulation hemostasis disorders. In essence, this variant of hemorrhagic diathesis is combined with elements of vasopathy, thrombocytopathy, and coagulopathy [3, 6, 22, 23].

Interesting hereditary thrombocytopathies include Bernard–Soulier syndrome, characterized by a defect in adhesion receptors GPIb-V-IX, and Glanzmann thrombasthenia, caused by a defect in aggregation receptors GPIIb/IIIa. Hereditary defects and deficiency of α-granules (gray platelet syndrome), deficiency of dense granules (Hermansky–Pudlak, Chediak-Higashi, Griscelli syndromes), defects in the phospholipids of the platelet membrane (Scott syndrome), etc. have been described [26, 35].

Acquired thrombocytopathy may occur against the background of uremia, paraproteinemia, and medication. A classic example is thrombocytopathy caused by aspirin. Aspirin blocks COX (cyclooxygenase), which reduces the synthesis of TxA_2 in platelets, which in turn leads to a decrease in secretion of platelet granule contents and a decrease in aggregation.

Blood coagulation disorders (coagulopathies) are caused primarily by hereditary and acquired coagulation factor deficiencies or impaired activity. Among hereditary coagulopathies, the most common, along with the above-mentioned von Willebrand disease, are hemophilia A and B, characterized by a deficiency and/or impaired activity of coagulation

factors VIII and IX, respectively. Both hemophilias are inherited in a recessive X-linked manner and are clinically manifested by a very characteristic hematoma type of bleeding with a predominance of hemorrhages into large joints of the extremities (hematoses), under skin, and in muscles [3].

One of the most common causes of acquired coagulopathies is vitamin K deficiency. This vitamin is fat-soluble, enters the body with food (greens, vegetables, beef liver, chicken meat), and is also formed by normal intestinal microflora. It is necessary for the formation of active coagulation factors X, IX, VII, II, as well as the activation of anticoagulants proteins C and S. The mechanism of vitamin K-dependent activation consists of Y-carboxylation of glutamic acid residues of these proteins. It is necessary for their binding to Ca2+ and phospholipids of platelet and endothelial membranes. Vitamin K deficiency in the patient's body can be associated with enteropathies and intestinal dysbacteriosis, impaired bile secretion and diseases of liver and pancreas, treatment with indirect anticoagulants [22].

Liver damage is the second most significant cause of acquired coagulopathies. Since the liver synthesizes most coagulation factors, liver disorders can lead to a deficiency of not only vitamin K-dependent factors, but also a number of others — V, I, XI, XIII.

Along with damage to coagulation system, increased bleeding can be caused by hereditary and acquired defects of fibrinolytic system, for example, hereditary deficiency of α_2-antiplasmin, excessive formation of plasminogen activators, and insufficient inactivation of plasminogen activators [23].

GENERAL CHARACTERISTICS OF THROMBOPHILIC SYNDROMES

Thrombophilias are hereditary and acquired disorders of hemostatic system, characterized by a predisposition to excessive, recurrent thrombus formation. It can be complicated by vascular obstruction with the development of ischemia and infarction (thrombosis in arteries) and venous congestion (thrombosis in veins), as well as thromboembolism, including its most formidable variant — pulmonary embolism (PE). In the 19th century, for understanding the mechanisms of thrombophilia, the so-called Virchow triad was formed. This triad is of enduring importance. According to the triad, to trigger the process of thrombus formation, the presence of at least one of three conditions is necessary: damage to the vascular wall, change in blood composition, and change in blood flow nature. Mechanisms of thrombophilia are always based on the action of one or more factors from this triad. The prominent Russian scientist Z.S. Barkagan, depending on causes and mechanisms, identified 10 groups of thrombophilic syndromes [4].

The first group includes so-called hemorheological forms, in which the tendency to thrombus formation is caused by blood thickening, as happens, for example, with true polycythemia.

The second group includes thrombophilias caused by an increase in the number of platelets and/or an increase in their adhesive and aggregation abilities. An increase in the number of platelets (thrombocytosis) can be primary (essential thrombocytosis) and secondary reactive, for example, in acute and chronic infections. An increase in adhesive and aggregation properties of platelets can be hereditary (syndrome of "viscous" platelets) and acquired (in diabetes mellitus). Adhesion and aggregation of platelets can also increase due to hyperproduction or insufficient degradation of VWF [8].

The third group included forms caused by hereditary and acquired deficiency of anticoagulants: AT (antithrombin), proteins C and S, and TFPI.

The fourth group includes forms caused by hyperproduction and anomalies of coagulation factors. Among these types of pathology, the most common is so-called Leiden mutation — a hereditary anomaly of factor V. It becomes resistant to the inhibitory action of protein C, as a result of which coagulation cascade is pathologically enhanced [27]. In the second place in frequency is hereditarily caused excess synthesis of coagulation factor II — prothrombin.

In the fifth group of thrombophilias, Z.S. Barkagan included pathologies of the hemostatic system caused by hereditary and acquired decrease in fibrinolysis caused by insufficient production of tPA by endothelium or increased production of TFPI.

The sixth group includes metabolic thrombophilias that occur in atherosclerosis, diabetes mellitus, and hyperhomocysteinemia. The leading mechanism is endothelial dysfunction, accompanied by a decrease in its thromboresistance [5, 18].

The seventh group includes autoimmune thrombophilias, among which the leading place is occupied by antiphospholipid syndrome. This syndrome occurs in systemic lupus erythematosus, chronic viral infections, lymphomas and is characterized by the formation of a large number of autoantibodies to phospholipids of endothelial cell membranes, activated platelets, monocytes. As a result, an imbalance in the hemostasis system occurs, in 75% of cases manifested by thrombophilia, in 25% — increased bleeding.

The eighth group includes paraneoplastic thrombophilias accompanying oncological diseases. In pathogenesis of paraneoplastic thrombophilias, an important role is played by mechanisms associated with the disruption of structural and functional integrity of the endothelium by tumor cells; activation of platelets by tumor cells; increased synthesis of procoagulants and fibrinolysis inhibitors by tumor cells;

and procoagulant activity of macrophages present in a tumor area [13].

The ninth group includes iatrogenic thrombophilia, for example, caused by taking hormonal contraceptives. Estrogens included in these drugs increase the synthesis of the number of coagulation factors (II, V, VII, IX, X, XI) [15].

The tenth group included thrombophilias that arose from a combination of several of the above-mentioned disorders. For example, the use of hormonal contraceptives by a patient with Leiden mutation increases the risk of venous thrombosis by 30–35 times, while the Leiden mutation itself increases the risk of thrombosis by 3–7 times [15, 27].

GENERAL CHARACTERISTICS OF THROMBOHEMORRHAGIC SYNDROME

In the study of thrombohemorrhagic syndrome, priority belongs to domestic researchers. In the first place are M.S. Machabeli, his colleagues and followers, who, since the 60s of the 20th century, have done a great deal of work to decipher its mechanisms and fully appreciate the general biological and general medical significance of this pathological process [3, 14].

Thrombohemorrhagic syndrome is represented in clinical practice by a number of pathologies. First of all, it is represented by DIC, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombotic thrombocytopenia, etc. Some diseases, referred to in this lecture as other types of hemostasopathies, for example, Henoch–Schönlein purpura and paraneoplastic thrombophilia, also gravitate towards thrombohemorrhagic syndrome in their pathogenesis [22, 27].

Thrombohemorrhagic syndrome is characterized by a phased total dynamic imbalance in all links of hemostatic system, which can be likened to the rocking the swing (pendulum), when all attempts of the body (and sometimes the attending physician) to stabilize the situation in most cases lead to even greater amplitude of deviations (Fig. 4).

The trigger mechanism of thrombohemorrhagic syndrome is hyperactivation of one of the links of the hemostasis system (coagulation, platelet, vascular) by exogenous and endogenous factors, leading to widespread, non-local, uncontrolled thrombus formation. In this case, natural endogenous mechanisms (thromboresistance of vascular wall, coagulation inhibitors, fibrinolytic system), providing local and reversible thrombosis, prove ineffective. Excessive widespread thrombus formation leads to characteristic consequences — ischemic damage to various organs, multiple organ failure. Subsequently, mechanisms of thrombus formation are depleted, the so-called consumption coagulopathy occurs, characterized by thrombocytopenia, deficiency of coagulation factors, activation of fibrinolytic system and clinically manifested by bleeding. This is the general picture of thrombohemorrhagic syndrome [3].

From the point of view of clinical practice, the most relevant and widespread variant of thrombohemorrhagic syndrome is DIC. It is always secondary and can develop as a complication of a wide range of diseases: sepsis (primarily

Рис. 4. Дисбаланс в системе гемостаза при тромбогеморрагическом синдроме
Fig. 4. Imbalance in the hemostasis system in thrombohemorrhagic syndrome

caused by gram-negative bacteria), a number of viral infections (including COVID-19), injuries, burns, surgeries, crush syndrome, massive hemolysis, pancreatitis, solid tumors, acute promyelocytic leukemia, obstetric pathology (premature placental abruption, amniotic fluid embolism, intrauterine fetal death), all types of shock, and poisonous snake bites. All of the above diseases are characterized by the release of a large number of procoagulants into blood, primarily TF. This leads to hypercoagulation with the generation of excess amounts of thrombin, activation of platelets, production of fibrin and the formation of a large number of thrombi in the vessels of the microvasculature of various areas [3, 9, 36, 37]. Conventionally, four stages of DIC syndrome are distinguished: Stage I — hypercoagulation and platelet activation; Stage II — transient with increasing coagulopathy and thrombocytopenia; Stage III — deep hypocoagulation caused by the consumption of coagulation factors and platelets; IV — recovery (or, in case of unfavorable course, the phase of outcomes and complications) [3, 14]. The course of DIC syndrome is quite diverse and can be both acute and chronic recurrent. The consequences are mainly reduced to the development of severe multiple organ failure (respiratory, renal, adrenal, hepatic) with a predominance of damage to various organs depending on characteristics of an underlying disease.

Treatment of DIC syndrome is one of the most complex and still not fully resolved problems. It is very important for a clinician to understand the dynamic, staged nature of thrombohemorrhagic syndrome. Just as when swinging a swing, the same impact in magnitude and direction, produced at different times, can either increase the amplitude of swinging or decrease it, so in treatment of DIC, the introduction of the same drug can have a beneficial effect if used in a timely manner and a harmful destructive effect if used untimely.

CONCLUSION

In conclusion, it is necessary to emphasize that with a high probability, almost every clinician will have to face the need to diagnose and treat hemostasis disorders. Success of treatment will largely depend on the doctor's understanding of pathophysiology of hemostasopathies.

ADDITIONAL INFORMATION

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

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IN MEMORY OF ALEXANDER PAVLOVICH AVTSYN

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Abstract. The article is devoted to the life and professional activities of the outstanding Soviet scientist-pathologist, academician of the USSR Academy of Medical Sciences, laureate of the State Prize, prizes named after I.V. Davydovsky, I.I. Mechnikov and the Moscow Society of Nature Testers, Doctor of Medical Sciences, Professor Alexander Pavlovich Avtsyn (13.09.1908–20.04.1993), born in Moscow into the family of an engineer and inventor. The working life of Alexander Pavlovich began at the age of 15, working in children's neuropsychiatric hospitals, while simultaneously studying at a Moscow secondary school, from which he graduated in 1925 As a 3rd year student and continuing to work in pathoanatomical laboratories, he became interested in scientific activities and in 1933, after successfully graduating from the 1st Moscow Medical Institute named after I.M. Sechenov, he got a job at the Institute of Neuropsychiatric Prevention of the People's Commissariat of Health of the RSFSR as a researcher under the guidance of Prof. P.E. Snesarev, where began studying the histopathology of the nervous system. In 1936, he defended his PhD dissertation, and in 1954, based on the collected material during the Great Patriotic War, defended his doctoral dissertation on the topic "Pathological anatomy of typhus". His scientific interests were issues of military and geographical pathology, pathological anatomy of infectious diseases, and cytopathology. He was distinguished by such traits as intelligence, charm, wit, the highest professionalism, a brilliant lecturer, and a polemicist. From 1961 to 1988, Alexander Pavlovich was the founder and first director of the Institute of Human Morphology, in whose post he founded and developed such scientific directions as geographical pathology and cytopharmacology, and from 1988 to 1993, he was an honorary adviser to the director of this institute. A.P. Avtsyn wrote more than 250 scientific papers, including monographs and chapters in manuals. A.P. Avtsyn died at the 85th year of his life from acute coronary insufficiency. He was buried at the Vagankovsky cemetery in Moscow. This and everything else is described in the presented article.

Keywords: Alexander Pavlovich Avtsyn, scientist-pathologist

ПАМЯТИ АЛЕКСАНДРА ПАВЛОВИЧА АВЦЫНА

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Резюме. Статья посвящена жизни и профессиональной деятельности выдающегося советского ученого-патолога, академика АМН СССР, лауреата Государственной премии, премий имени И.В. Давыдовского, И.И. Мечникова и Московского общества испытателей природы, доктора медицинских наук, профессора Александра Павловича Авцына (13.09.1908–20.04.1993), родившегося в Москве в семье инженера и изобретателя. Трудовая жизнь Александра Павло-

вича началась в 15-летнем возрасте, когда он работал в детских нейропсихиатрических лечебницах и одновременно учился в Московской средней школе, которую окончил в 1925 г. Будучи студентом 3-го курса и продолжая работать в патологоанатомических лабораториях, увлекся научной деятельностью, и в 1933 г. после успешного окончания 1-го Московского медицинского института имени И.М. Сеченова устроился работать в Институт нейропсихиатрической профилактики Наркомздрава РСФСР научным сотрудником под руководством проф. П.Е. Снесарева, где приступил к изучению гистопатологии нервной системы. В 1936 г. защитил кандидатскую диссертацию, а в 1954 г. на материале, собранном во время Великой Отечественной войны, — докторскую диссертацию на тему «Патологическая анатомия сыпного тифа». Его научными интересами были вопросы военной и географической патологии, патологической анатомии инфекционных болезней, цитопатологии. Его отличали такие черты, как интеллигентность, обаятельность, остроумие, высочайший профессионализм, он был блестящим лектором, полемистом. С 1961 по 1988 гг. Александр Павлович основал, а затем был первым директором Института морфологии человека, на посту которого обосновал и развил такие научные направления, как географическая патология и цитофармакология, а с 1988 по 1993 гг. — был почетным советником директора этого института. Перу А.П. Авцына принадлежит более 250 научных работ, в том числе монографий и глав в руководствах. А.П. Авцын скончался на 85-м году жизни от острой коронарной недостаточности. Похоронен на Ваганьковском кладбище г. Москвы. Об этом и обо всем другом повествуется в представленной статье.

Ключевые слова: Александр Павлович Авцын, ученый-патолог

On September 13th, 2023 we have celebrated the 115th anniversary birth, and April 20 — the 30th anniversary of death to the outstanding Soviet scientist-pathologist, pathophysiologist, neurohistologist, cytologist, educator and organizer, academician of the USSR Academy of Medical Sciences, laureate of the State Prize, prizes named after I.V. Davydovsky, I.I. Mechnikov and the Moscow Society of Nature Testers, Doctor of Medical Sciences, Professor Alexander Pavlovich Avtsyn [1] (Fig. 1, 2).

Alexander Pavlovich Avtsyn was born on September 13, 1908 in Moscow in the family of a talented engineer and inventor in the field of telephone business and electric motors Pavel Ivanovich (1919 death) and housewife Maria Alexandrovna (amazingly beautiful woman with kind eyes, 1889–1949) Avtsyn.

Sasha Avtsyn began his working life back in 1923 at the age of 15, giving lessons, working in kindergartens and children's neuropsychiatric hospitals, while simultaneously

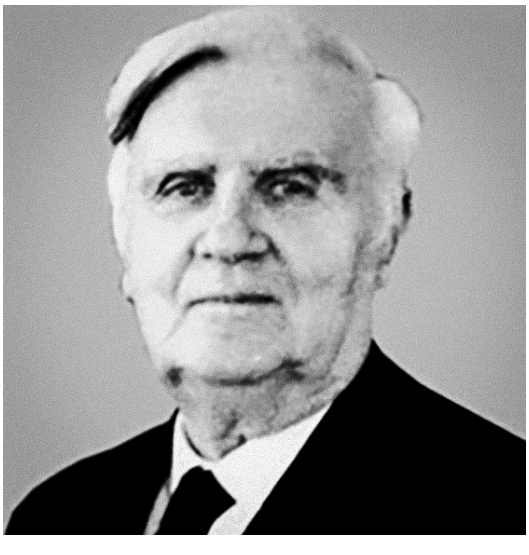

Fig. 1. **Alexander Pavlovich Avtsyn (13.09.1908 — 20.04.1993) (Available at: http://www.morfolhum.ru/about/history/ (accessed 31.10.2023))**

Рис. 1. **Александр Павлович Авцын (13.09.1908 — 20.04.1993) (Доступно по: http://www.morfolhum.ru/about/history/ (дата обращения: 31.10.2023))**

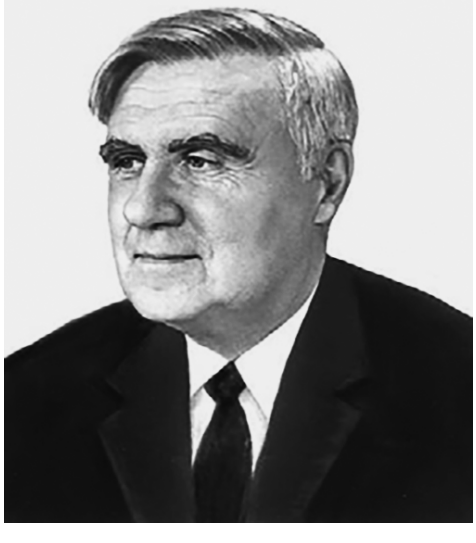

Fig. 2. **Alexander Pavlovich Avtsyn (Available at: https://edu.monikiweb.ru/istoria-v-litsah.php?p=atabekov-david-nersesovich) (accessed 31.10.2023))**

Рис. 2. **Александр Павлович Авцын (Доступно по: https://edu.monikiweb.ru/istoria-v-litsah.php?p=atabekov-david-nersesovich) (дата обращения: 31.10.2023))**

studying at Moscow Secondary School No. 41, from which he graduated in 1925. His non-proletarian origin prevented him from further realizing his dream of becoming a doctor, and only after the personal support of the first People's Commissar of Education of the RSFSR Anatoly Vasilievich Lunacharsky, a stubborn young man in 1929 was still able to enter the medical faculty of Nizhny Novgorod State University. In 1930, student Avtsyn transferred to the Mother See for the 2nd year of the 1st Moscow Medical Institute (1MMI) named after I.M. Sechenov, which he successfully graduated in 1933 [2].

A.P. Avtsyn's scientific interests throughout his bright life were the issues of histopathology of the nervous system, military and geographical pathology, pathological anatomy of infectious diseases, cytopathology and others. He was distinguished by such traits as intelligence, goodwill, charm, wisdom, wit, the highest professionalism with encyclopedic erudition, an excellent storyteller, a brilliant lecturer and polemicist, acute perception of the new and clinical intuition, especially manifested in expeditions. He often liked to repeat a phrase such as "we have nothing original," which in turn can correspond and be recognized as his motto (creed) [3].

A man of science, Alexander Pavlovich, at the same time, never closed himself within the framework of his profession and throughout his life was fond of literature, theater, fine arts, and composing his own poems. Probably, A.P. Avtsyn inherited a craving for travel and expeditions from his father, which he was so clearly able to realize later during his research into human geographic pathology [4].

As a 3rd year student, continuing to work, in particular, as a laboratory assistant in pathoanatomical laboratories (PAL) and being carried away by scientific activities, from 1933 to 1937 he got a job as a researcher at the PAL of the Institute of Neuropsychiatric Prevention of the People's Commissariat of Health of the RSFSR (now the Federal State Budgetary Institution "National Medical Research Center for Psychiatry and Narcology named after V.P. Serbsky" of the Ministry of Health of the Russian Federation) under the leadership of Professor P.E. Snesarev, where he enthusiastically began studying the histopathology of the nervous system, combining this position with external work in Moscow prosecturas under the leadership of Yu.M. Lazovsky and V.A. Klirikova. As a result of this study, in 1936 he gave the first description of mesoglioblastomas arising in children from embryonic microglioblasts and in the same year A.P. Avtsyn defended his dissertation for the degree of Candidate of Medical Sciences, and the observations, looking ahead, collected by him in during the Great Patriotic War (GPW), gave him the opportunity to defend his doctoral dissertation in 1954 on the topic "Pathological anatomy of typhus," which made it possible to create a new concept of this disease [5].

Earlier, in 1939, he proposed an original method for staining myelin fibers in the central nervous system by impregnating histological sections of the brain with phosphorus-molybdenum silver — the Avtsyn method. Long-term research

Fig. 3. In Berlin, near the walls of the Reichstag, the end of the Great Patriotic War. A.P. Avtsyn (left), next to his wife Vera Alexandrovna Rykova. (Available at: https://roim.historymed.ru/science/publications/8098/ (accessed 31.10.2023))

Рис. 3. В Берлине у стен Рейхстага, конец Великой Отечественной войны. А.П. Авцын (слева) рядом с женой Верой Александровной Рыковой. (Доступно по: https://roim.historymed.ru/science/publications/8098/ (дата обращения: 31.10.2023))

on the pathology of typhus and other rickettsioses in collaboration with Prof. M.M. Mayevsky allowed A.P. Avtsyn not only to confirm the classical data of I.V. Davydovsky, but also to develop and supplement them in many ways with new observations of fundamental importance, in particular, his description of protracted forms of typhus, which ended fatally as a result of allergic vascular lesions the brain or the heart, and in 1942 he described a valuable diagnostic sign of typhus – a conjunctival rash called the "Chiari–Avtsyn symptom" and proposed an adrenaline test to identify it, and in 1944 he described peculiar cells in the brain stem, givung rise to special transfascicular fibers — Avtsyn fibers, some of which end near the cerebral vessels [6].

A.P. Avtsyn discovered the formation of a specific capsule in the tissues of experimental animals around a pill of a polycyclic aromatic hydrocarbon, which is a strong carcinogen: dimethylbenzanthracene (DMBA) — the Avtsyn capsule phenomenon. The villous cells in this capsule were named after him. In addition, in 1946, using pathohistological method, he established the angioparalytic effect of Provacek's rickettsia toxin and the elimination of this effect under the influence of specific antibodies. Examining the fine structure of central nerve fibers, Alexander Pavlovich showed that they, like peripheral ones, have Ranvier intercepts or their morphological analogues [7].

After graduating from the institute, A.P. Avtsyn also worked as an assistant, then as an associate professor at the Department of Pathological Anatomy of the I MMI, and in 1934 he began working as an assistant prosector at the Moscow Clinical Institute of Infectious Diseases. From 1937 to 1941, he was an assistant, associate professor at the Department of Pathological Anatomy of the 3rd MMI. From 1942 to 1943 — Acting Associate Professor at the Department of Pathological Anatomy of the I MMI.

During the GPW, A.P. Avtsyn was drafted into the ranks of the Red Army (date of commencement and completion of service: 03.1943 — 09.24.1945). With the rank of military doctor 3rd rank (now major of medical service) as part of the active army of the South-Western, 3rd Ukrainian and 1st Belorussian fronts, he headed the pathoanatomical service of the triage evacuation hospital No. 2613, evacuation hospital No. 3642, then PAL of the central research center clinical hospital of the Soviet Army. By the way, in 1943 A.P. Avtsyn managed to create a family unit by marrying Vera Alexandrovna Rykova, they had no children. The war ended in Berlin, near the walls of the Reichstag (Fig. 3). His wife V.A. Rykova (03.07.1904 — 10.11.1994) was born in Moscow (start and end date of service: 23.03.1943 — 04.07.1946). With the rank of captain of the medical service as part of the 3rd Ukrainian Front, 3rd Guards Army, 1st Belorussian Front, she served in triage evacuation hospital No. 2613, had awards: medals "For the Defense of Moscow", "For the Victory over Germany in the Great Patriotic War" Patriotic War of 1941–1945" [8–10].

During the GPW, A.P. Avtsyn's attention was focused on the study of the pathology of combat trauma. He collected a large pathological material (2500 observations), on the basis of which he developed the pathological anatomy of gunshot osteomyelitis, infectious and alimentary dystrophy of the wounded, anaerobic pleural infection, tetanus, wound sepsis, complications of gunshot wounds. In 1946, his monograph "Essays on military Pathology" was awarded a prize at the state competition of scientific papers summarizing the experience of military medicine during the GPW [11].

In front-line conditions, A.P. Avtsyn for the first time studied the morphological picture of the effect of the first domestic antibiotics together with academician Z.V. Ermolyeva. Using a large material, he showed the positive effect of streptomycin in tuberculous meningitis, expressed in the disappearance of the exudative component with an increase in the productive reaction. In the field of experimental pathology A.P. Avtsyn proposed new methods for modeling dysentery, typhoid, colibacillary, staphylo-, strepto- and pneumococcal, tuberculosis and leishmanial pneumonia in mice in order to study the chemotherapeutic effect of various antibiotics [12].

From 1945 to 1951 A.P. Avtsyn was a senior researcher at the Laboratory of Pathological Anatomy of Childhood Diseases of the Institute of Normal and Pathological Anatomy of the USSR Academy of Medical Sciences under the leadership of the head of this laboratory, Academician of the USSR Academy of Medical Sciences M.A. Skvortsov, who was his true teacher and Alexander Pavlovich considered the happiest years of work under his leadership at this institute.

In 1950, by order of the Minister of Health of the USSR A.P. Avtsyn was transferred to the Research Laboratory at the Mausoleum of V.I. Lenin and from 1951 to 1961 was the head of the morphological department of this laboratory, where he carried out extensive scientific and organizational work to strengthen the morphological department, as well as training young specialists in the field of theory and practice of embalming. He was directly involved in the embalming and preservation of Georgy Dimitrov's body in Sofia. For the successful fulfillment of the responsible task of the Government and for his work in the laboratory at the Lenin Mausoleum, A.P. Avtsyn was awarded the Order of Lenin, and the Government of the People's Republic of Bulgaria awarded him the Order "Red Banner of Labor" [13].

From 1955 to 1961, A.P. Avtsyn was part-time head of the morphological department of PAL with the prosectorium of the Institute of Neurosurgery named after N.N. Burdenko of the USSR Academy of Medical Sciences.

In October 1958, A.P. Avtsyn was sent by the USSR Ministry of Health to Switzerland for a meeting of the WHO expert committee. At this meeting, Alexander Pavlovich for the first time expressed his point of view that regional and geographical patho-

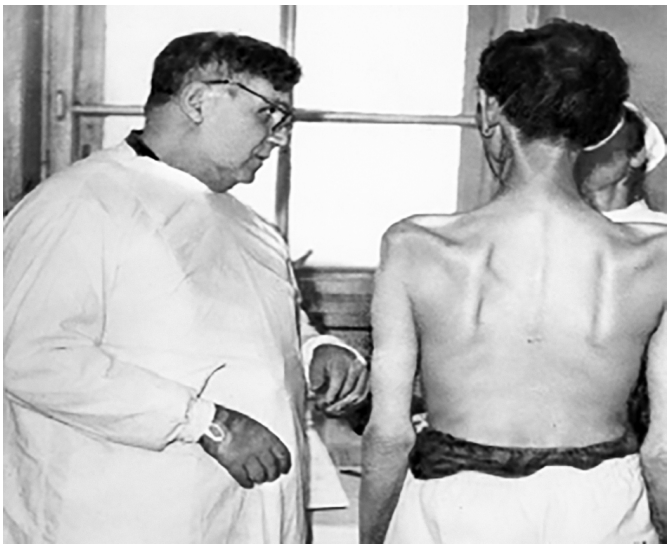

Fig. 4. Examination by A.P.Avtsyn of a patient in the neurological department of the Murmansk Regional Hospital. (Available at: https://roim.historymed.ru/science/publications/8098/ (accessed 31.10.2023))

Рис. 4. Осмотр А.П. Авцыным больного неврологического отделения Мурманской областной больницы. (Доступно по: https://roim.historymed.ru/science/publications/8098/ (дата обращения 31.10.2023))

Fig. 5. A.P. Avtsyn is in a cheerful mood — the meeting of the Scientific Council of the Institute of Human Morphology is going well. (Available at: https://roim.historymed.ru/science/publications/8098/ (accessed 31.10.2023))

Рис. 5. У А.П. Авцына хорошее настроение — заседание Ученого совета Института морфологии человека проходит хорошо. (Доступно по: https://roim.historymed.ru/science/publications/8098/ (дата обращения: 31.10.2023))

logy are two different organizational forms of one science — medical ecology. The scientist also believed that geographical pathology in many ways resembles military pathology. He explained that "severe forms of regional diseases, as a rule, arise in extreme climatogeographical, medical-biological and social conditions. The unfavorable effects of these conditions on a person and his body, on the one hand, cause extreme tension in the adaptation mechanisms, and on the other hand, they conceal the possibility of disadaptation, which can manifest itself in certain forms of weakening of the body, leading to the occurrence of diseases that end in death or premature disability. Therefore, "this is undoubtedly a complex science or even a system of sciences, presenting the greatest opportunities for a multidisciplinary approach."

In 1960, he experimentally proved the effect of hormones on the development of some brain tumors and showed their differences in the content of sexual chromatin, and in 1963 formulated the main provisions of theoretical neurooncology, introduced the concept of preglyoma for the first time and discovered the preproliferative period in certain types of chemical carcinogenesis in the central nervous system.

In the mid-70s, after a cholera outbreak in the south of the country, A.P. Avtsyn studied in depth the cellular mechanisms of cholera intoxication and NAG infection. In particular, he obtained fundamentally new results that made it possible to explain the "rapid intestinal dehydration syndrome", and in 1979 he described the nature of ultrastructural changes in organs under a number of pathogenic influences.

From 1961 to 1988, A.P. Avtsyn was the founder and first director of the Scientific Research Institute of Human Morphology (SRIHM) of the USSR Academy of Medical Sciences in Moscow. In this position, Alexander Pavlovich theoretically justified and developed scientific directions in our country — geographical pathology and cytopharmacology, which he paid great attention to not only within the walls of his institute. Under his leadership and with his personal participation, numerous and long-term expeditionary studies were carried out in the regions of the Far and Near North, the Baikal-Amur Mainline zone, arid zones and highlands, both in our country (Fig. 4) and beyond its borders, in particular the Equatorial Africa. The results of these studies were presented in the form of recommendations aimed at improving disease prevention in the geographic areas studied. He was the first to describe such forms of regional pathology as Kola encephalitis, Magadan pneumopathy, and identified the northern variant of hypertension. That is why A.P. Avtsyn should rightfully be considered one of the recognized leaders of the large school of domestic geographical pathologists, covering many specialties. It should be noted that the SRIHM was organized on the basis of order of the USSR Ministry of Health No. 495 dated November 28, 1960 and began its activities in early 1961, initially located on the basis of the pathology department (PD) of a large multidisciplinary clinical institution — Moscow Regional Research Institute named after M.F. Vladimirsky, where from 1961 to 1973

A.P. Avtsyn headed the PD, which at that time was located in the 13th building of this institute, and at the same time was the director SRIHM. In 1973, SRIHM started its activities in its own building at a new location on Tsyurupy Street [14].

From 1968 to 1969, after the death of I.V. Davydovsky, the Department of Pathological Anatomy of the 2nd MMI named after N.I. Pirogov was headed by Academician of the USSR Academy of Medical Sciences A.P. Avtsyn. From 1988 to 1993, A.P. Avtsyn was an honorary adviser to the director of the SRIHM of the USSR Academy of Medical Sciences (now the Research Institute of Human Morphology named after Academician A.P. Avtsyn of the Federal State Budgetary Scientific Institution "Russian Scientific Center for Surgery named after Academician B.V. Petrovsky").

A.P. Avtsyn is the author of more than 250 scientific works, including monographs and chapters in manuals. Such works as "Essays on Military Pathology" (1946), "Pathological Anatomy of Typhus" (1954), "Pathological Anatomy of Diseases Caused by Rickettsias" (1964), "Introduction to Geographical Pathology" (1972) and the first modern domestic manual on cell pathology "Ultrastructural Foundations of Cell Pathology" (1978), written by A.P. Avtsyn together with Prof. V.A. Shakhlamov, in which his concepts of pathogenic information, its reception by the cell, the stages of this process and its significance for the initiation of any disease were further developed.

A.P. Avtsyn was one of the WHO experts to create a new classification of the brain oncological diseases, took an active part in the USSR Academy of Sciences commission on applied human physiology, in the Presidium of the USSR Academy of Sciences Scientific Council on microelements, was a member of the Presidium of the All-Union and the Board of the Moscow Society of Pathologists, editorial board of the journals "Arkhiv Pat ologii", "Bulletin of the USSR Academy of Medical Sciences", "Human Physiology", Soviet Committee on the UNESCO Problem "Man and the Biosphere", organizer and honorary chairman of the Moscow Scientific Society of Cytologists, chairman of the Scientific Council of Union significance "Human Morphology", author and editor of the editorial departments "Pathology and Morphology", "Psychiatry" and "Pathological Anatomy" of the 2nd and 3rd editions of the Great Medical Encyclopedia, Small and Brief Medical Encyclopedias, and also headed the Scientific Council on Human Morphology of the USSR Academy of Medical Sciences for over 10 years (Fig. 5). Over 80 PhD and doctoral dissertations have been completed under his supervision.

A.P. Avtsyn's achievements and his great contribution to science were highly appreciated by the state. In 1961, he was elected a corresponding member, and in 1965, an academician of the USSR Academy of Medical Sciences. In 1982 — laureate of the USSR State Prize for a series of works in the field of geographical pathology and epidemiology of cardiovascular, oncological and nervous diseases, in 1985 — laureate of the I.V. Davydovsky Prize for the collective monograph "Human Pathology in the North", in 1990 — laureate of the I.I. Mechnikov Prize for a series of works "Pathology of Infectious Diseases", and was also awarded two Orders of Lenin, two Orders of the Red Banner of Labor, the Order of the Patriotic War, II degree, and many military and labor medals [15].

In recent years, A.P. Avtsyn has paid much attention to the medical microelementology, the allocation of which is a logical continuation of the classical studies of academician V.I. Vernadsky. The accumulated original material with world literature data on this issue was systematized in 1991 in the collective monograph "Human microelementoses (etiology, classification, organopathology)", and in 1994 this book was awarded the first prize of the oldest Moscow Society of Natural Scientists in the country.

Fig. 6. The tombstone monument to Alexander Pavlovich Avtsyn on the family plot of the Vagankovsky cemetery in Moscow. Photo by Evgeny Danilov (2014). (Available at: http://mednecropol.ru/a/avtzyn-ap/avtzyn-ap.htm (accessed 20.08.2023))

Рис. 6. Надгробный памятник Александру Павловичу Авцыну на родовом участке Ваганьковского кладбища в Москве. Фото Евгения Данилова (2014). (Доступно по: http://mednecropol.ru/a/avtzyn-ap/avtzyn-ap.htm (дата обращения: 20.08.2023))

A.P. Avtsyn died suddenly on April 20, 1993 in Moscow at the 85th year of his life from acute coronary insufficiency. He was buried at the Vagankovsky cemetery (site 34) of the capital (Fig. 6) [16] . On the basis of the order of the Ministry of Education and Science of the Russian Federation dated 27.07.2021, No. 687, the Scientific Research Institute of Human Morphology was named after Academician A.P. Avtsyn.

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TO THE 100TH ANNIVERSARY OF AVENIR MIKHAILOVICH YAKOVLEV

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Abstract. The article is dedicated to Professor Avenir Mikhailovich Yakovlev (1923–1994), Doctor of Medical Sciences, who headed the Department of Microbiology, Virology and Immunology of the Leningrad Paediatric Medical Institute (LPMI) for 15 years (1974–1989). He had to overcome many difficulties and shocks to become a prominent scientist and teacher, colonel of medical service, educator of several generations of civilian and military doctors. The loss of his priest father in childhood during political repressions, injury at the beginning of the war during the evacuation of the Military Medical Academy (MMA) from Leningrad, studies at a military paramedical school, participation on various fronts in Red Army combat operations, studies at the MMA, service in the Transbaikal Military District, adjuncture and subsequent scientific and pedagogical work at the MMA — these are the main milestones of his biography until he joined the LPMI in 1974. The article evaluates the main scientific and pedagogical achievements of A.M. Yakovlev in different periods of his activity and his contribution to the training of paediatricians.

Keywords: Professor A.M. Yakovlev, military service, microbiology, scientific and pedagogical work, family history

К 100-ЛЕТИЮ СО ДНЯ РОЖДЕНИЯ ПРОФЕССОРА АВЕНИРА МИХАЙЛОВИЧА ЯКОВЛЕВА

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Резюме. Статья посвящена доктору медицинских наук, профессору Авениру Михайловичу Яковлеву (1923–1994), который 15 лет (1974–1989) заведовал кафедрой микробиологии, вирусологии и иммунологии Ленинградского педиатрического медицинского института (ныне СПбГПМУ). Ему довелось преодолеть немало трудностей и потрясений, чтобы стать видным ученым и педагогом, полковником медицинской службы, воспитателем нескольких поколений гражданских и военных врачей. Потеря в детстве отца-священника в ходе политических репрессий, ранение в начале войны при эвакуации Военно-медицинской академии (ВМА) из Ленинграда, учеба в военно-фельдшерском училище, участие на разных фронтах в боевых действиях Красной армии, учеба в ВМА, служба

в Забайкальском военном округе, адъюнктура и последующая научно-педагогическая работа в ВМА — таковы основные вехи его биографии до прихода в 1974 г. в ЛПМИ. В статье дана оценка основным научно-педагогическим достижениям А.М. Яковлева в разные периоды деятельности и его вкладу в подготовку врачей-педиатров.

Ключевые слова: профессор А.М. Яковлев, военная служба, микробиология, научно-педагогическая работа, история семьи

In 2023, we celebrated the 100th anniversary of the outstanding Soviet microbiologist Professor Avenir Mikhailovich Yakovlev. Avenir Mikhailovich's life path was not easy. He was born in Leningrad to the family of priest Mikhail Nikolaevich Yakovlev, who served in the Church of the Resurrection of Christ Church also known as the Church of the Savior on Spilled Blood and in The Church of the Resurrection of Christ near the Warsaw Railway Station on an embankment of Obvodniy canal. It was a time of active persecution of church ministers and religion in general. In recently published memoirs of two sisters, witnesses of that period in life of the church, we find the following: "We see ourselves in the elegant Church of the Resurrection. The light from chandeliers, lamps and candles flickers and shimmers in a multitude of mosaics and in the icon frames... Our father stands on a pulpit in vestments and a kamilavka with a cross in his hands. The dark-haired protodeacon Father Mikhail Yakovlev will serve with our father. Sons of Father Mikhail, our friends Arkady and Avenir, in brocade sticharions, will serve during the bishop's service" [1]. Those who heard Father Michail read and sang noted his outstanding vocal abilities and keen musical ear; the protodeacon's baritone bass with its bright timbre truly adorned the church service.

In 1930, both churches were closed, but even earlier, some of the church ministers were arrested and shot, while others were sent to camps or exiled outside of Leningrad. Archdeacon Yakovlev was among them: after his arrest and imprisonment, there was hard labor on the construction of the White Sea-Baltic Canal, then exile to the remote town of Malaya Vishera in the Novgorod region with a ban on leaving its borders. After the Germans occupied these places, he moved mostly on foot to Prague, and then to Vienna, where he continued his ministry. Only in 1953, he was able to return to his homeland. Until his retirement, he served as a protodeacon in the Pavlovsk Cathedral in Gatchina, and then in the Church of the Intercession of the Holy Mother of God in Marienburg near Gatchina.

After graduating from high school in 1941, A.M. Yakovlev entered the Military Medical Academy named after S.M. Kirov, which was soon evacuated. First, there was a many-kilometer hungry march to the opposite shore of Lake Ladoga and further to the railway station. The train with cadets traveling to the east was hit by German bombs. Cadet Yakovlev suffered a severe concussion, there was a suspicion of a fracture of skull base. Periodically losing consciousness, he nevertheless endured the entire long way to Samarkand. Now, the academy was stationed there. Because of a cranial injury, studying was very difficult. Therefore, in 1942, he was transferred for further treatment and study to the Kharkov Military Paramedic School, in Ashgabat.

After completing an accelerated course of paramedic training, in August 1943, with the rank of lieutenant of the medical service, he was sent to the front. He took part in military operations on the Voronezh, 2nd Ukrainian and 3rd Belorussian fronts. In 1945, his military unit was redeployed to the Far East to participate in the war with Japan and the liberation of North Korea. Only in 1947, medical lieutenant Yakovlev was able to re-enroll in the 1st year of the Military Medical Academy named after S.M. Kirov. After graduating in 1953, he was sent for further service in forces of the Far Eastern Military District (Irkutsk).

As a student at the Academy, A.M. Yakovlev worked enthusiastically in the scientific circle at the Department of Microbiology and managed to carry out independent research on the competition of bacterial antigens. His interest in scientific work was noticed by the management, two years later he passed a competition and entered a postgraduate program at this department.

During all subsequent years of service at the Military Medical Academy, A.M. Yakovlev carried out extensive teaching and research work. He successively held positions of adjunct professor, research fellow at the thermal injury clinic, junior lecturer, lecturer and senior lecturer at the microbiology department of the Military Medical Academy named after S.M. Kirov. In 1958, he defended his candidate thesis on the experimental study of aerosol injury with botulinum toxin and the development of specific means of protection against it [2]. In 1967, his doctoral thesis, which became a fundamental study of microbiology of burn infection, was done [3]. In the last years of his military service, in addition to his main activities, he performed the function assigned to him as the head of the educational department, skilfully organizing the educational process of a large teaching staff. At the end of 1973, he retired from the army with the rank of colonel of the medical service (Fig. 1). In January 1974, he was elected

head of the microbiology department of the Leningrad Pediatric Medical Institute. In 1975, he received the academic title of professor.

In the new place, Professor Yakovlev paid great attention to the study of current problems of clinical microbiology and immunology. The department began to actively participate in joint research with clinics of the institute. Under his leadership, the department's staff (Fig. 2) performed a number of original studies on characteristics of children's immunity in normal and pathological conditions (I.D. Annenkova, V.V. Turkin, L.G. Velikosel'tseva, L.M. Ishchenko, A.P. Khoruzhko, T.V. Tolmazova, N.S. Movchan, I.V. Drobot), microbiology and immunology of purulent-septic infections in full-term and premature infants (N.N. Kaplin), and the development of new methods for immunodiagnostics of tuberculosis (E.A. Stepanova). During this period, several textbooks were published for students of the Leningrad Pediatric Medical Institute and pediatric faculties of other medical institutes [4–6]. A.M. Yakovlev is the author of more than 130 scientific papers and the scientific supervisor of 9 candidate theses.

Avenir Mikhailovich gave lectures on all areas of microbiology, virology and immunology. He always vividly sought to reveal the history of the development of microbiology, virology and immunology, showing the current state and prospects for the development of these sciences, their

Fig. 1. Colonel of Medical Service A.M. Yakovlev (1973)
Рис. 1. Полковник медицинской службы А.М. Яковлев (1973)

Fig. 2. The Staff of the Department of Microbiology, Virology and Immunology (1985). From left to right sitting: K.I. Smirnova, A.M. Yakovlev, E.A. Stepanova; standing: O.V. Golishcheva, L.G. Velikoseltseva, N.N. Kaplin, I.D. Annenkova, V.V. Turkin, A.A. Shamarova, A.P. Horuzhko, L.M. Ishchenko, T.V. Tolmazova

Рис. 2. Коллектив кафедры микробиологии, вирусологии и иммунологии (1985). Слева направо сидят: К.И. Смирнова, А.М. Яковлев, Э.А. Степанова; стоят: О.В. Голищева, Л.Г. Великосельцева, Н.Н. Каплин, И.Д. Анненкова, В.В. Туркин, А.А. Шамарова, А.П. Хоружко, Л.М. Ищенко, Т.В. Толмазова

relationship with other disciplines. Being a deep connoisseur of fiction and history, he skilfully used this knowledge in the pedagogical process. Students listened to his lectures with particular interest, they attracted them to the student scientific society at the department. Some subsequently linked their professional activities with microbiology, many of his students still work in various universities and research institutes in Russia and abroad. Professor A.M. Yakovlev carried out a great deal of pedagogical work at the faculty of advanced education. Surely, many current employees of SPSPMU, who studied at our university at that time, gratefully remember Avenir Mikhailovich. In 1973, for the successful training of doctors, he was awarded a certificate from the Ministry of Higher and Secondary Specialized Education of the USSR.

He paid considerable attention to methodological work, being the deputy chairman of the methodological council of the Institute and the chairman of the educational and methodological commission of the Leningrad Society of Epidemiologists, Microbiologists and Parasitologists. A veteran of the Great Patriotic War, a member of the CPSU, a colonel of the medical service, he was awarded two Orders of the Red Star, the Medal “For Courage” and 13 other medals.

In conclusion, a few words about the family environment of A.M. Yakovlev. As noted above, his mother Zinaida Pavlovna was left alone with three children after her husband was arrested. Over the course of many years, despite the circumstances of her life, she performed a truly maternal feat, raising her sons firmly on their feet: the eldest, Arkady, is a famous monumental artist, the youngest, Arian, is a doctor of geological and mineralogical sciences, professor at the Mining Institute, and Avenir became a military microbiologist, a prominent scientist and teacher. Zinaida Pavlovna, being a teacher of Russian language and literature at school since 1914, selflessly gave all her talent as a philologist and educator to her students. It is no coincidence that for her many years of successful pedagogical work she was awarded the Order of Lenin, the highest state award of the USSR, which was given for especially outstanding services to the state and society.

During Avenir Mikhailovich’s service at the Military Medical Academy, a terrible tragedy occurred — his wife Svetlana Dmitrievna, also, by the way, a bacteriologist, died in a plane crash in 1962, practically before his eyes. However, this did not break him, he was able to raise a worthy member of society from the child left in his arms. He was helped in this by the support of his second wife, Zoya Konstantinovna Kolb. Until her recent retirement, she had worked actively for many years as a researcher, teacher and practical virologist-mycologist at the Military Medical Academy and in other medical institutions of our city.

Now Alexey Avenirovich Yakovlev is a famous Russian infectious disease doctor, a major organizer of domestic healthcare, Doctor of Medical Sciences, Professor, Honored Doctor of the Russian Federation. For more than 25 years he was the chief physician of the largest hospital of this profile in Russia — the S.P. Botkin Clinical Infectious Diseases Hospital. He put a lot of effort and energy into organizing the construction, equipping and launching new buildings of the famous Botkin Infectious Diseases Hospital in the north of St. Petersburg. During the COVID-19 pandemic, it was the city institution that took on the brunt of the workload. A.A. Yakovlev continues to head the Department of Infectious Diseases, Epidemiology and Dermatovenereology at the Faculty of Medicine of St. Petersburg State University, which he founded in 1997.

The authors had the honor and pleasure of closely communicating with Avenir Mikhailovich Yakovlev both during his military service and during his work at LPMI.

He will forever remain in the memory of his colleagues and students as a talented scientist and teacher, an intelligent and charming person of exceptional kindness and cheerfulness, who devoted all his efforts to the development of science and education of qualified military doctors and pediatricians.

ADDITIONAL INFORMATION

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

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 05.04.24

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «**Russian Biomedical Research»** (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), свидетельство: ПИ № ФС77-74228 от 02 ноября 2018 г. (ранее ПИ № ТУ78-01869 от 17 мая 2016 г.), именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

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Рукопись считается поступившей в Редакцию, если она представлена комплектно и оформлена в соответствии с описанными требованиями. Предварительное рассмотрение рукописи, не заказанной Редакцией, не является фактом заключения между сторонами издательского Договора.

При представлении рукописи в Журнал Авторы несут ответственность за раскрытие своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

Правила оформления статей к публикации

Статья предоставляется в электронной форме (файл MS Word версии не старше 2003, т.е. с расширением doc), шрифт — 14, интервал — полуторный.

Файл статьи называется по Фамилии первого автора, например, Иванов.doc или Petrov.doc. Никаких других слов в названии не должно быть!

Ориентировочные размеры статьи, включая указатель литературы, таблицы и резюме, — 10–12 страниц текста через полтора интервала или 20–25 тысяч знаков с пробелами. Рекомендуемый размер обзора — 18–20 страниц «машинописного» текста или 35–40 тысяч знаков с пробелами. Примерное число литературных ссылок для экспериментальной статьи — 20, для обзоров и проблемных статей — 50.

Файл статьи должен содержать
НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ:

- Заглавие (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.
- Сведения об авторах (публикуются). Для каждого автора указываются: фамилия, имя и отчество, место работы, почтовый адрес места работы, e-mail, ORCID, SPIN-код. Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях, или по системе BGN (Board of Geographic Names), см. сайт http://www.translit.ru.
- Резюме (Abstract) (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

  Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Russian Biomedical Research» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

  Рекомендуемая структура как аннотации, так и самой статьи IMRAD (для оригинальных исследований структура обязательна): введение (Introduction), материалы и методы (Materials and methods), результаты (Results), обсуждение (Discussion), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. **Объем текста авторского резюме** определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах **200–250 слов (1500–2000 знаков)**.
- Ключевые слова (Keywords) от 3 до 10 ключевых слов или словосочетаний из 2–4 слов, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «Ключевые слова». Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются запятой.
- Текст статьи может быть написан либо на русском, либо на английском языке, также возможна публикация статьи с полным переводом. На русском и английском языках необходимо предоставить все рисунки и таблицы (заголовки, все надписи, а также текст таблиц должны иметь перевод).

  В разделе «Методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

  Таблицы и рисунки приводятся непосредственно в теле статьи, каждый из которых имеет номер и название с обязательными ссылками на них в тексте статьи — в контексте предложения (например: «…как показано на рисунке 1…») или в конце предложения в круглых скобках (например: «...выявлена положительная корреляционная связь умеренной степени (r=0,41) между уровнем ТТГ матери и новорожденного (рис. 2)»; просьба учитывать, что в печатной версии журнала рисунки будут воспроизводиться в черно-белом варианте.
- Список литературы обязательно приводится в порядке упоминания.

Текст статьи должен быть подготовлен в строгом соответствии с настоящими правилами и тщательно выверен автором. В случае обнаружения значительного количества опечаток, небрежностей, пунктуационных и орфографических ошибок, нерасшифрованных сокращений, отсутствия основных компонентов, переводов заголовков таблиц, подрисуночных подписей, надписей на рисунках,

текста таблиц и других технических дефектов оформления статей редакция возвращает статью автору для доработки. Небольшие погрешности редакция может исправить сама без согласования с автором. Редакция оставляет за собой право осуществления литературного и технического редактирования статей.

Сокращений, кроме общеупотребительных, следует избегать. Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть непременно расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

Все цитирования производятся следующим образом:

ФИО автора, год издания и прочая информация не упоминаются в тексте. Вместо этого указывается ссылка на источник литературы в виде номера в квадратных скобках (пример: «Ряд исследователей отмечает различные нарушения речевых функций при эпилепсии в детском возрасте [17, 21, 22].»), который включен в расставленный в порядке упоминания (1, 2, 3 и т.д.) список источников в конце статьи.

Все ссылки должны иметь соответствующий источник в списке, а каждый источник в списке — ссылку в тексте.

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И.О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы. (Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное) ухо» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в переведенном на английский язык (References).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в порядке упоминания.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

Приказы, нормативные акты, методические письма и прочие законные акты, патенты, полезные модели не вносятся в список литературы, оформляются в виде сносок. Сноска — примечание, помещаемое внизу страницы (постраничная сноска). Знак сноски ставят цифрой после фрагмента основного текста, где есть упоминание об этих источниках. Рекомендуется сквозная нумерация сносок по тексту.

Интернет-ресурс

1. Интернет-ресурс, где есть название источника, автор, вносится в список литературы (в порядке алфавита) с указанием даты обращения (см. ниже пример оформления).

2. Если есть только ссылка на сайт, оформляется подстрочное примечание (сноска), с указанием даты обращения.

Щеглов И. Насколько велика роль микрофлоры в биологии вида-хозяина? Живые системы: научный электронный журнал. Доступен по: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (дата обращения 02.07.2012).

Kealy M. A., Small R. E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/47/ (accessed 11.09.2013).

Примеры оформления литературы

Книга:

Юрьев В.К., Моисеева К.Е., Глущенко В.А. Основы общественного здоровья и здравоохранения. Учебник. СПб.: СпецЛит; 2019.

Никифоров О.Н., ред. Санкт-Петербург в 2021 году. СПб.: Петростат; 2022.

Brandenburg J.H., Ponti G.S., Worring A.F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY:Mosby; 1998.

Domeika M. Diagnosis of genital chlamydial infection in humans as well as in cattle. Uppsala; 1994.

Глава из книги:

Тутельян В.А., Никитюк Д.Б., Шарафетдинов Х.Х. Здоровое питание — основа здорового образа жизни и профилактики хронических неинфекционных заболеваний. В кн.: Здоровье молодежи: новые вызовы и перспективы. Т. 3. М.; 2019: 203–227.

Статья из журнала:

Карсанов А.М., Полунина Н.В., Гогичаев Т.К. Безопасность пациентов в хирургии. Часть 2: Программа менеджмента качества хирургического лечения. Медицинские технологии. Оценка и выбор. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065.

Brandenburg J.H., Ponti G.S., Worring A.F. Vocal cord injection with autogenous fat: a long-term magnetic resona. Laryngoscope. 1996;l06(2,pt l):174–80.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2012;39(5):574–580.

Тезисы докладов, материалы научных конференций:

Марковская И.Н., Завьялова А.Н., Кузнецова Ю.В. Микробный пейзаж пациента первого года жизни с дисфагией, длительно находящегося в ОРИТ. XXX Конгресс детских гастроэнтерологов России и стран СНГ: тез. докл. М.; 2023: 29–31.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». Ч. 1. М.; 2000; 516–519.

Авторефераты:

Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. … канд. психол. наук. СПб.; 2021.

Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: https://rosstat.gov.ru/folder/12781 (дата обращения: 23.10.2023).

World Health Organization. Prevalence and incidence of selected sexually transmitted infections — 2008. Geneva: World Health Organization; 2012. Available at: https://aefsg.ch/wp-content/uploads/who-9789241503839_eng.pdf (accessed 11.04.2024)

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

Если цитируемая статья написана **на латинице** (на английском, немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования. Пример (статья в норвежском журнале на норвежском языке):

Ellingsen A.E., Wilhelmsen I. Sykdomsangst blant medisinog jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

Стандарт транслитерации. При транслитерации рекомендуется использовать стандарт BSI (British Standard Institute, UK). Для транслитерации текста в соответствии со стандартом BSI можно воспользоваться ссылкой http://ru.translit.ru/?account=bsi.

ФИО авторов, редакторов. Фамилии и инициалы всех авторов на латинице следует приводить в ссылке так, как они даны в оригинальной публикации. Если в оригинальной публикации уже были приведены на латинице ФИО авторов, в ссылке на статью следует указывать именно этот вариант (независимо от использованной системы транслитерации в первоисточнике). Если в официальных источниках (на сайте журнала, в базах данных, в том числе в eLIBRARY) ФИО авторов на латинице не приведены, следует транслитерировать их самостоятельно по стандарту BSI.

Название публикации. Если у цитируемой Вами работы существует официальный перевод на английский язык или англоязычный вариант названия (его следует искать на сайте журнала, в базах данных, в том числе в eLIBRARY), следует указать именно его. Если в официальных источниках название публикации на латинице не приведено, следует выполнить транслитерацию в романский алфавит по стандарту BSI.

Название издания (журнала). Некоторые не англоязычные научные издания (журналы) имеют кроме названия на родном языке официальное «параллельное» название на английском (например, у журнала «Сахарный диабет» есть официальное англоязычное название «Diabetes Mellitus»). Таким образом, для списка References в ссылке на статью из русскоязычного журнала следует указать либо транслитерированное название журнала, либо переводное. Переводное название журнала можно взять либо с официального сайта журнала (или использовать данные о правильном написании англоязычного названия из цитируемой статьи), либо проверить его наличие в базе данных, например в CAS Source Index, библиотеке WorldCat или каталоге Web of Science (ISI), каталоге названий базы данных MedLine (NLM Catalog). В случае, когда у журнала нет официального названия на английском языке, в References нужно приводить транслитерацию по системе BSI. Не следует самостоятельно переводить названия журналов.

Место издания. Место издания в ссылках всегда следует указывать на английском языке и полностью — не в транслитерации и без сокращений. То есть Moscow, а не «Moskva» и не «M.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. В отличие от места издания, название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Примеры перевода русскоязычных источников литературы для англоязычного блока статьи

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract. report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma “Mat’ i ditya”. Part 1: Moscow; 2000; 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: https://rosstat.gov.ru/folder/12781 (accessed: 10/23/2023). (In Russian).

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Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547-52. EDN: YRAEPZ.

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ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

Руководство по педиатрии. ОФТАЛЬМОЛОГИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.В. Бржеский

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Издание предназначено офтальмологам, педиатрам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

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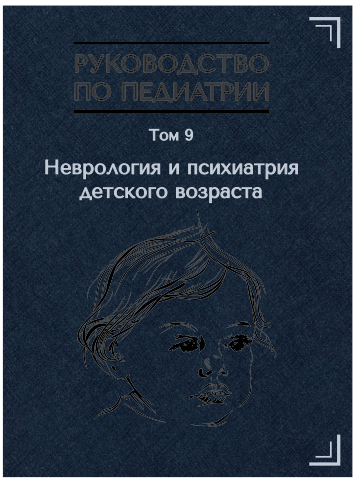
Редакционная коллегия тома: Д.О. Иванов, В.И. Гузева, С.В. Гречаный



Том 9 «Руководства по педиатрии» отражает современный уровень развития неврологии и психиатрии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний нервной системы и психических расстройствах. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

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ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

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

Учебник соответствует программе Министерства здравоохранения Российской Федерации по ортопедической стоматологии, предназначен и будет полезным для преподавателей курсов и стоматологических кафедр, студентов стоматологических факультетов, ординаторов, аспирантов, врачей-стоматологов.

Авторы будут признательны за критические замечания и дополнения.

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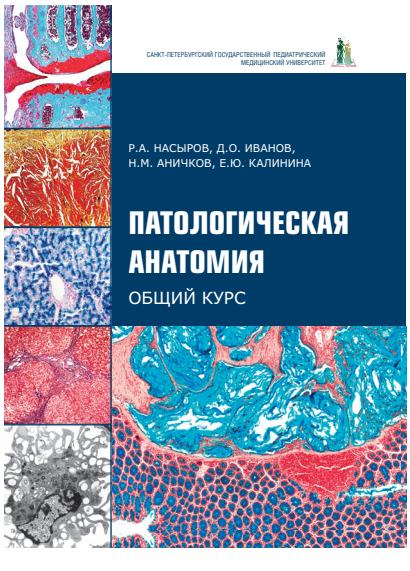
ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. ОБЩИЙ КУРС

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



В общем курсе патологической анатомии (клинической патоморфологии) рассмотрены вопросы общей патологической анатомии: методы исследования в патоморфологии, повреждение и гибель клеток и тканей, в том числе старение; нарушения кровообращения и иных сред организма, воспаление, репарация и регенерация, заживление ран, иммунная патология, адаптация, патология роста клеток и их дифференцировки, опухоли, генетические заболевания, учение о диагнозе в патологической анатомии, патология и факторы окружающей среды, патология, вызванная питанием, констатация смерти и др.

Учебник рассчитан на студентов-медиков всех факультетов, а также на врачей, интересующихся вопросами общей патологической анатомии.

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