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New view on the compatibility of hemoglobin function in the erythrocytes

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ABSTRACT

Aim: To study the process of hemoglobin oxidation and the enzymatic reactions associated with it.

Materials and Methods: Heparinized human blood (15 IU/ml) was obtained from the clinical department. The concentration of oxy- and methemoglobin, auto-oxidation of hemoglobin was determined spectrophotometrically spectrophotometrically. Autooxidation of hemoglobin was recorded spectrophotometrically, and protein concentration was determined by the Lowry method. Monooxygenase activity of hemoglobin was also measured by the method described by Lowry spectrophotometrically. The concentration of O_2 and H_2O_2 in the reaction media was determined on a biomicroanalyzer OR 210/3 (Redelkis).

Results: The obtained experimental data allow us to propose a mechanism of "spontaneous autooxidation" of oxyhemoglobin, which can be described by the following equations:

$Hb^{2+}O_2 \longrightarrow Hb^{3+} + O_2^-$ (1)

$Hb^{2+}O_2 + 2e^- + 2H^+ \longrightarrow Hb^{3+} + H_2O_2$ (2)

$Hb^{2+}O_2 + 2e^- + 2H^+ \longrightarrow Hb^{2+} + H_2O_2$ (3)

$Hb^{2+} + O_2 \longrightarrow Hb^{2+}O_2$ (4)

Spectral characteristics of the process of "spontaneous auto-oxidation" indicate the formation of a metform of hemoglobin, the depletion of oxygen by the system was established, at pH 5.6, an increase in the monooxygenase activity of hemoglobin is observed 3-4 times compared to the physiological level.

Conclusions: In addition to the main, previously known functions of hemoglobin (gas transport, peroxidase, monooxygenase), it catalyzes a two-electron oxidase reaction in which O_2 is reduced to H_2O_2. This is confirmed by experimental data on the formation of one of the products of "spontaneous autoxidation" of oxyhemoglobin _ deoxyform at pH 5.6 _ 8.9.

KEY WORDS: oxyhemoglobin, methemoglobin, autooxidation, monooxygenase activity, oxidase reaction, ligands

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INTRODUCTION

The hemoglobin molecule in erythrocytes can undergo oxidation (autooxidation) or be oxidized by other factors, losing the ability to carry oxygen. The concentration of methemoglobin (metHb) in a healthy person usually does not exceed 1% of the total amount of hemoglobin. This level of methemoglobin is the result of a balance between methemoglobin formation and its recovery. In patients with diaphorase I (methemoglobin reductase) deficiency, about 3% of total hemoglobin is oxidized every day [l-3].

The reversibility of the binding of the ligands of the prosthetic group of hemoglobin is due to a protein component that forms a specific environment for heme, which in turn prevents its oxidation. However, subtle exchange of ligands (O2, 2,3-DFH, NO) would be impossible in the presence of rigid protection of the prostaglandin group. Ligands reach the active center of hemoglobin as a result of coordinated small-scale fluctuations of certain side groups of amino acid residues of the globule (β-93), which ensure the reduction of the internal molecular barrier and the formation of the trajectory of the ligand in the direction of heme [4]. It should be noted that in conditions of cessation of oxygen access from the external environment, oxyhemoglobin is capable of autooxidation due to oxygen, which is bound to heme iron [5].

The analysis of literature data allows us to conclude that the exact mechanism of spontaneous oxidation is unknown, and the explanations that exist today are quite contradictory [5]. None of the known works present data on the formation of reduced hemoglobin, which under certain conditions is a transitional form in the process of spontaneous autoxidation of its

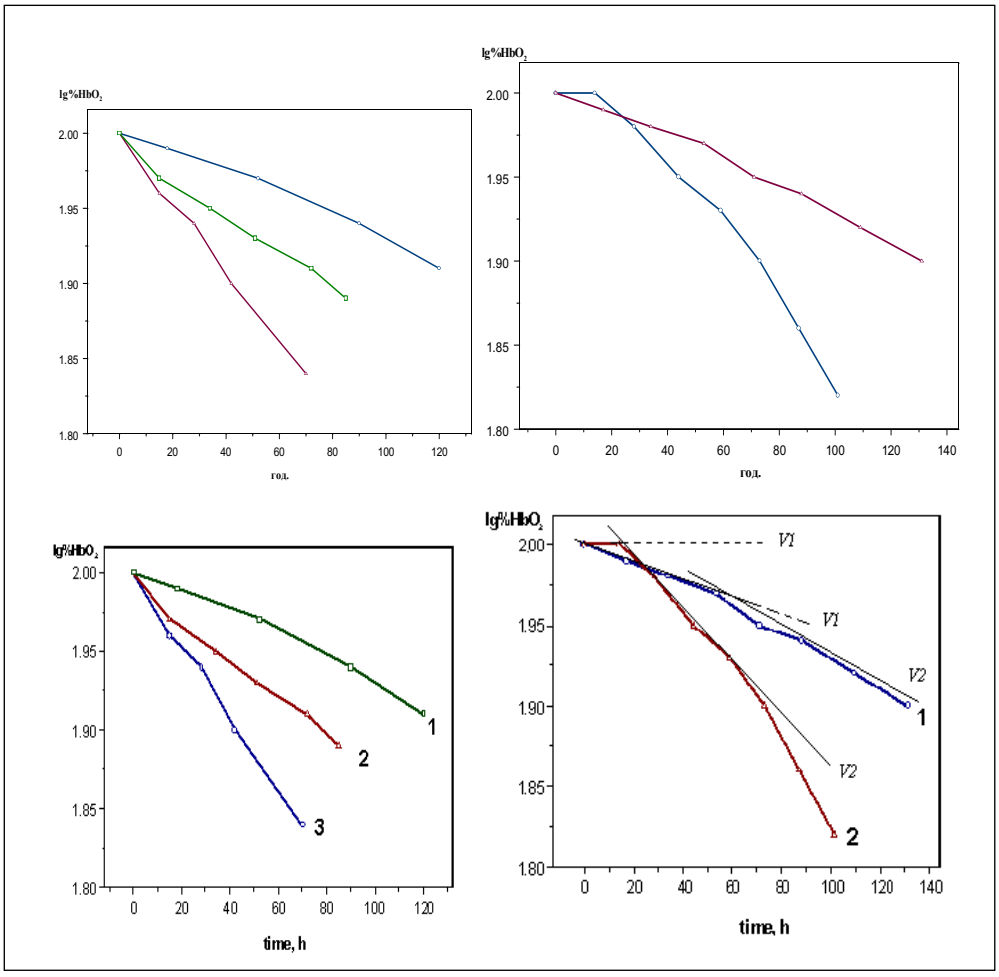

Fig. 1A. Kinetics of the spontaneous autooxidation of the human hemoglobin.
Reaction medium (3,0 ml 0,1 M acetate buffer pH 5,6) contained 0,001M EDTA and 50 – 60 μmoll oxyhemoglobin. 1. – oxyhemoglobin not purified from low-molecular ligands; 2 – oxyhemoglobin purified from low-molecular ligands; 3 – oxyhemoglobin purified from low-molecular ligands and 2,3-DPG. Temperature of reaction medium - 37°C. n = 5, p< 0,05;
B. Kinetics of the spontaneous autooxidation of the human hemoglobin. Reaction medium (3,0 ml 0,05 M tris-HCl buffer pH 7,2) contained 0,001M EDTA and 50 – 60 μmoll oxyhemoglobin. 1. – oxyhemoglobin not purified from low-molecular ligands; 2 – oxyhemoglobin purified from low-molecular ligands. Temperature of reaction medium - 37°C. n = 5, p< 0,05.

prosthetic group. In connection with the above, the study of the process of hemoglobin oxidation and the enzymatic reactions associated with it is relevant today.

AIM

The purpose of our research is to study the process of hemoglobin oxidation and the enzymatic reactions associated with it.

MATERIALS AND METHODS

Experiments were conducted with human hemoglobin, which was isolated from peripheral blood and purified [6, 7]. Heparinized human blood (15 IU/ml) was obtained from the clinical department of Danylo Halytskyi Lviv National Medical University. The concentration of oxy- and methemoglobin was determined spectrophotometrically [8]. Autooxidation of hemoglobin was recorded spectrophotometrically [2], and protein concentration was determined by the Lowry method. Monooxygenase activity of hemoglobin was also measured by the method described by Lowry spectrophotometrically [7]. The concentration of O_2 and H_2O_2 in the reaction media was determined on a biomicroanalyzer OR 210/3 (Redelkis).

RESULTS

The detected products of the "spontaneous autoxidation" reaction indicate the previously not fully understood and unknown properties of hemoglobin. Thus, oxyhemoglobin is able to "spontaneously autoxidize" into metform through a reaction, the speed of which depends on the degree of its purification from low molecular weight compounds (Fig. 1A). With an increase in pH, that is, at physiological values, the kinetics of the rate of "spontaneous autoxidation" of oxyhemoglobin has a complex nature and is characterized by rates V1 and V2 (Fig. 1B). For the first time, it was shown spectrophotometrically that at physiological pH values, when "spontaneous autoxidation" occurs, in addition to metform, the deoxyform of hemoglobin is also formed. This is evidenced by the absorption spectra of hemoglobin after depressurization of the cuvettes (Fig. 2A, B).

As can be seen, low-molecular compounds on the one hand activate "spontaneous auto-oxidation", and on the other - protect oxyhemoglobin from oxidation to met-

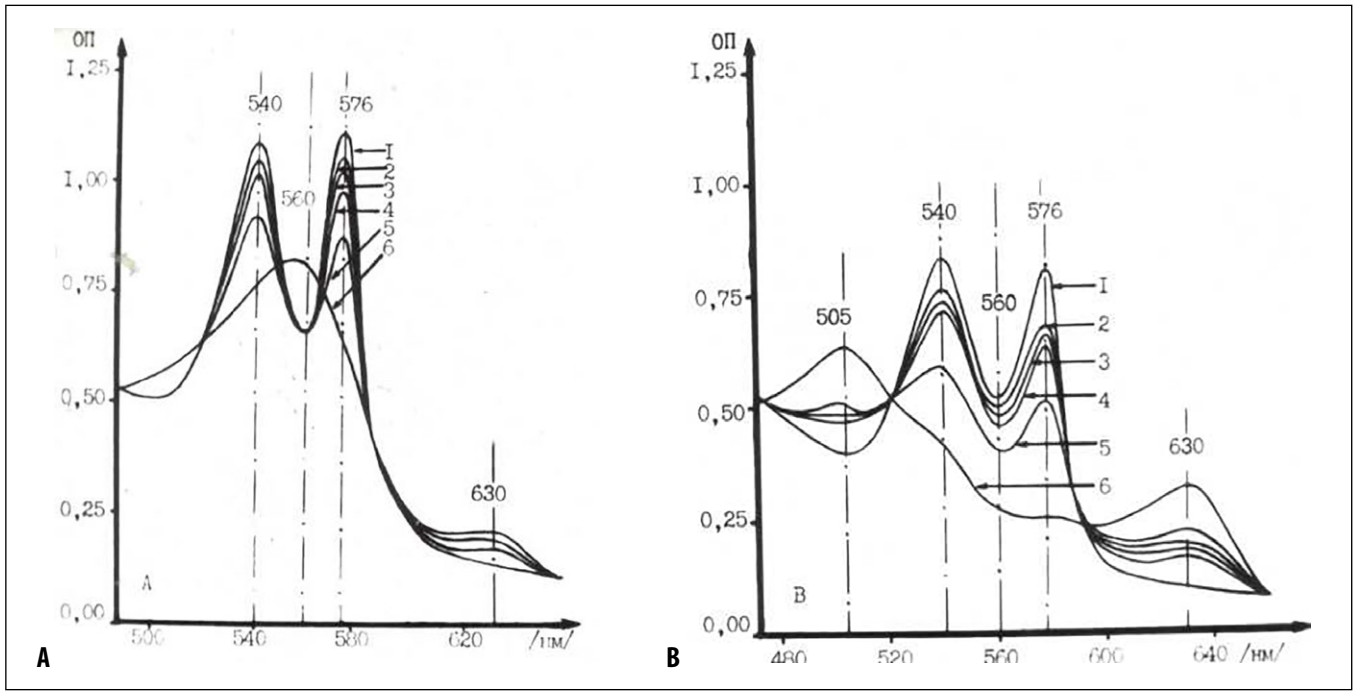

Fig. 2. A. Specters of absorbtion of hemoglobin with low-molecular ligands. Spectra were obtained after 1 _ 24 hours, 2 _ 48 hours, 3 _ 72 hours; 4 _ 96 hours, 5 _ 120 hours, 6 _ 144 hours;
B. Specters of absorbtion of hemoglobin purified from low-molecular ligands. Spectra were obtained after 1 _ 24 hours, 2 _ 48 hours, 3 _ 72 hours; 4 _ 96 hours, 5 _ 120 hours, 6 _ 144 hours

form. Therefore, low-molecular-weight compounds at physiological pH values take a direct part in stabilizing the conformational state of the hemoglobin molecule, that is, stimulating its "spontaneous auto-oxidation", while not changing the oxidation-reduction state of iron in the heme structure. This is not observed when pH decreases, in particular at pH 5.6.

In addition to the already known, such a protective system is the ingredient low-molecular composition of the erythrocyte. Thus, at physiological pH, complete oxidation of oxyhemoglobin to metform does not occur, and after depressurization of the cuvettes, oxygenation of deoxyhemoglobin is observed. Hemoglobin, which contains low-molecular-weight compounds, is oxygenated faster compared to purified hemoglobin (Fig. 2A).

The obtained experimental data, as well as information from the literature [8], allow us to propose a mechanism of "spontaneous autoxidation" of oxyhemoglobin, which can be described by the following equations:

$Hb^{2+}O_2 \longrightarrow Hb^{3+} + O_2^-$ (1)

$Hb^{2+}O_2 + 2e^- + 2H^+ \longrightarrow Hb^{3+} + H_2O_2$ (2)

$Hb^{2+}O_2 + 2e^- + 2H^+ \longrightarrow Hb^{2+} + H_2O_2$ (3)

$Hb^{2+} + O_2 \longrightarrow Hb^{2+}O_2$ (4)

During hemolysis of erythrocytes (extracellular) hemoglobin can enter the bloodstream, where the concentration of antioxidant enzymes is low, and act as a source of iron ions, which is not active in oxyhemoglobin. Hydrogen peroxide, hypochlorous acid, organic lipid hydroperoxides can modify oxyhemoglobin with the formation of more reactive compounds _ feryl and perferrylhemoglobin [23]. Hemoglobin modification products by oxidants are able to cause peroxidation of lipids, blood lipoproteins, lipids of biomembranes [24] and other important biomolecules of the body [25], thus being the cause of the occurrence and development of various diseases.

Mechanisms of cellular and extracellular hemoglobin oxidation, as well as the influence of factors on cellular and extracellular "spontaneous autooxidation" of hemoglobin are presented in Fig 3 and Fig 4.

At a pH value of 5.6, reactions 1-4 occur, because, firstly, the spectral characteristics of the process of "spontaneous autoxidation" indicate the formation of the metform of hemoglobin (reactions 1, 2), and secondly, it is established that the system is depleted of oxygen (reactions 3, 4), thirdly, at this pH there is an increase in the monooxygenase activity of hemoglobin by 3-4 times compared to the physiological level.

DISCUSSION

Blood hemoglobin is always at risk of oxidation to methemoglobin, in which the molecule retains its original structure but can no longer carry oxygen.

It is believed that part of the oxygenated hemoglobin HbFe2+O2 is located in the form of $HbFe^{3+}O_2$-. [4]:

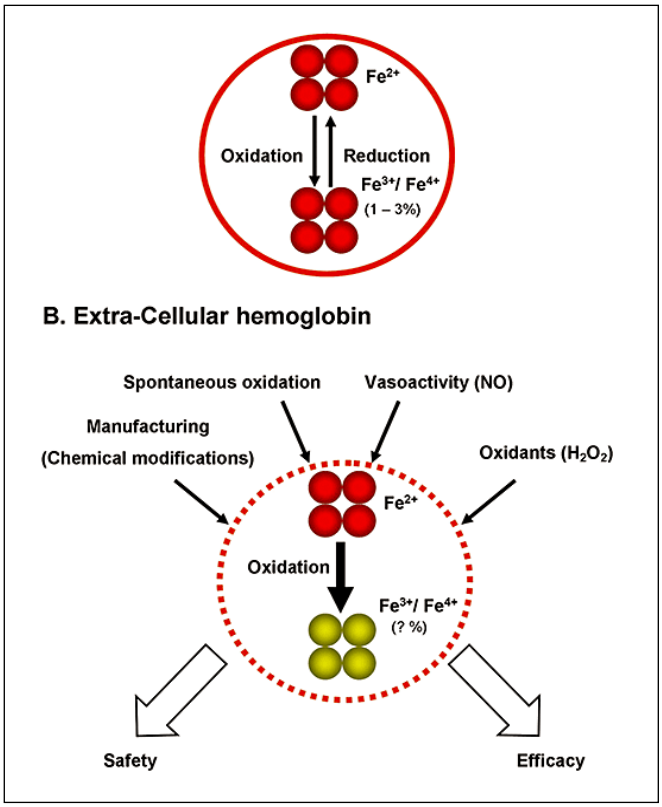

Fig. 3. Factors influencing cellular and acellular hemoglobin oxidation. The schematic represents reductive processes of (A) cellular and (B) extra-cellular hemoglobin. In (A) the oxidation followed by enzymatic and non enzymatic processes in the red blood cell lead to minimal accumulation of $HbFe^{3-}$and $HbFe^{4+}$. The physical barrier of the red cell membrane (red circle) limits NO and H_2O_2 mediated oxidative processes. In (B) when the protective mechanisms of the red blood cell are eliminated such as is the case with HBOCs or when Hb is released, the influences of enzymatic/non-enzymatic reductive processes are lost allowing for an unknown amount of oxidized hemoglobin accumulation. Moreover each arrow indicates processes, which may directly lead to the accumulation of oxidized Hb.

$HbFe^{2+}O_2 \leftrightarrow HbFe^{3+}\ O_2$-.(1)

(the initial stage of autoxidation corresponds to the dissociation of this form into methemoglobin ($HbFe^{3+}$) and O_{2-} (superoxide anion):

$HbFe^{3+}O_2^{-\cdot} \rightarrow HbFe^{3+} + O_2^{-\cdot}$ (2) [1, 4, 5]

formed by O2-. attacks the new oxyhemoglobin molecule in the presence of H+ ions (low pH):

$HbFe^{2+}O_2 + O_2^{-\cdot} + 2H^+ \rightarrow HbFe^{3+} + H_2O_2 + O_2$ (3)

The resulting H_2O_2 [3] attacks the new oxyhemoglobin molecule:

$HbFe^{2+}O_2 + H_2O_2 \rightarrow HbFe^{3+}\ OH\cdot + OH^- + O_2$ (4)

OH the radical that is formed from oxyhemoglobin can then react with other oxyhemoglobin molecules:

$HbFe^{2+}O_2 + OH\cdot \rightarrow HbFe^{3+} + 2OH^- + O_2$ (5)

Peroxides react with oxyhemoglobin $HbFe^{+}O_2$ or methemoglobin with formation of protein-associated oxidant type ($HbFe^{4+}$) and dangerous peroxide radicals [6, 7, 8-13].

$HbFe^{2+}O_2 + H_2O_2 \rightarrow HbFe^{4+}OH + OH\cdot + O_2$ with formation O_2 (5)

$HbFe^{3+} + H_2O_2 + H^+ \rightarrow HbFe^{4+}OH + H_2O$ (6)

In erythrocytes, this highly toxic protein radical reacts with $HbFe^{2+}O_2$:

$HbFe^{4+} + HbFe^{2+}O_2 \rightarrow 2HbFe^{3+} + O_2$ (7)

The formed methemoglobin is restored (reduced) by methemoglobin reductase [14-18].

In addition to self-oxidation, hemoglobin can be oxidized by the superoxide radical (O^{2-}), which is constantly generated in erythrocytes [l] and in all aerobic cells [16]:

$O_2 + e^- \rightarrow O_2^{-\cdot}$(8)

This radical can affect the oxidation of oxyhemoglobin to methemoglobin [4].

Hemoglobin can be oxidized by nitric oxide, which is produced by endothelial cells and released into the

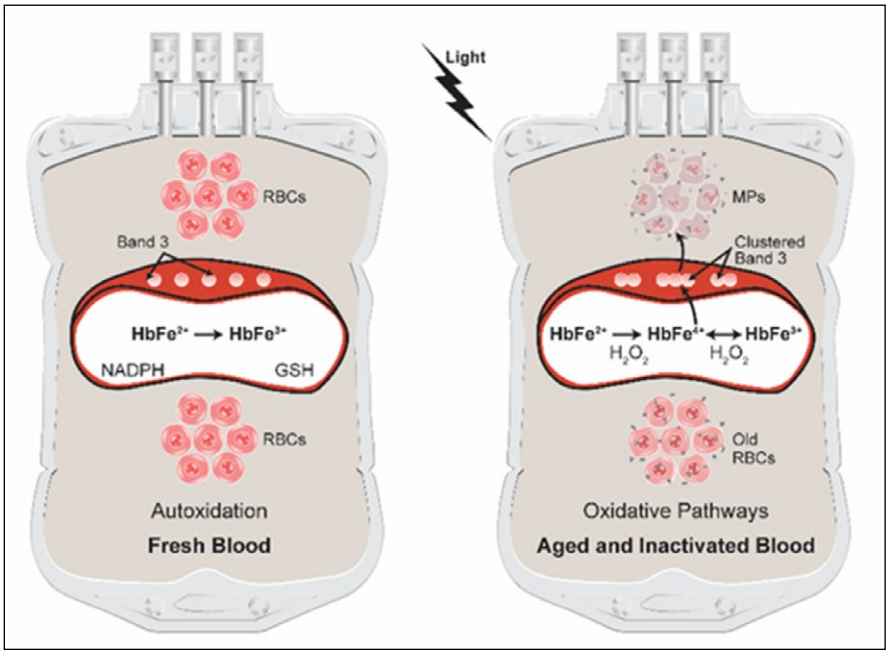

Fig. 4. Oxidative damage of erythrocytes during storage and conditions of pathogen inactivation. Freshly stored RBCs in a standard blood bag undergo very little oxidation apart from normal spontaneous (autoxidation) reactions of Hb, resulting in little metHb accumulation (left). Reductive and antioxidant enzymes/proteins such as NADPH reductase and GSH maintain metHb to a minimum. Under prolonged storage conditions or when RBCs are exposed to UV light, Hb oxidative side reactions are increased, mainly Hb's own pseudoperoxidative pathways (right). These pathways result in the production of ferryl Hb ($HbFe^{4+}$) which attacks other biological targets including band 3, resulting in band 3 clustering. Ferryl Hb crosslinks the major RBC membranes band 3 into clusters and the ultimate release of Hb-laden microparticles (MPs), based on with modifications.

Table 1. Antioxidant enzymes and concentrations of reducing agents in human plasma and erythrocytes [17].

Concentration	Plasma	Erythrocytes
Antioxidant Enzymes	(U ml^{-1})	(U-10^{-10} cells)
Superoxide dismutase	5-20	550-800
Catalase	?	3800-5400
(GSH) peroxydase	0.4	7.8 -10.6
(GSSG) reductase	0.0	2.7-3.7
Reducing Agents	μM	μM
Glutathione (GSH)	5	2.5 $l0^3$ to 10 $l0^3$
Ascorbic acid	45 to 85	40 to 70

bloodstream, and can enter the erythrocyte. Thus, hemoglobin will probably be oxidized as follows [4]:

$2HbFe^{2+}O_2 + 2{\cdot}NO + e^- \rightarrow 2HbFe^{3+} + 2NO_2{\cdot} + O_2^{-}{\cdot}$ (9)

or by the equation:

$2{\cdot}NO + O_2 \rightarrow 2{\cdot}NO_2$ (12) [24]:

$HbFe^{2+}O_2 + {\cdot}NO_2 \rightarrow HbFe^{3+} + NO_2^- + O_2$ (10)

As a result of the reaction, the nitrite anion NO_2- is formed, which reacts with a new molecule of oxyhemoglobin in an acidic environment:

$HbFe^{2+}O_2 + 2H^+ + NO_2^- \rightarrow HbFe^{3+} + {\cdot}NO_2 + H_2O_2$ (11) [19]

or by the equation:

$HbFe^{2+}O_2 + {\cdot}NO \rightarrow HbFe^{3+} + NO_3^-$ (15) [20].

H_2O_2 and O_2- are formed. can react with a new molecule of oxyhemoglobin according to reactions 3-4. Hemoglobin in erythrocytes or in blood plasma would not perform the function of oxygen transfer if there was no enzymatic system to inhibit its oxidation reactions.

Reactions limiting hemoglobin oxidation [21].

Since superoxide anion and hydrogen peroxide are naturally formed in the body, there are enzyme systems that protect hemoglobin from oxidation: superoxide dismutase to neutralize superoxide anion (O_2^-), glutathione peroxidase and catalase to split H_2O_2 [5, 13, 22]. The activity of these enzymes is high in erythrocytes and low in blood plasma [23].

Erythrocytes contain enzymatic or non-enzymatic systems that restore the hemoglobin molecule to its active form and physiological function, keeping the level of circulating methemoglobin below 1%. Methhemoglobin recovery pathways are mainly enzymatic and associated with erythrocyte glycolysis (Table 1).

Superoxide dismutase (SOD) catalyzes the reaction:

Superoxide dismutase

$2O_2^{-}{\cdot} + 2H^+ \rightarrow H_2O_2{\cdot} + O_2$ (12)

Low concentrations of H2O2 are mainly decomposed by glutathione peroxidase [18, 24]:

Glutationperoxidase

$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$ (13)

Then, as the decomposition of high concentrations of H2O2 is catalyzed by catalase:

Catalase

$H_2O_2 \rightarrow H_2O + ½\ O_2$ (14)

These reactions depend mainly on hydrogen sources, such as NAD and NADPH [23, 26, 27].

An important supplier of hydrogen is the NAD-dependent metabolic pathway associated with anaerobic glycolysis. NAD is reduced to NADH, which is then used by methemoglobin reductase (diaphorase I, NADH dehydrogenase, or cytochrome b5 reductase [25, 27].

Cytochrome b5-reductase

$NADH + Cytb_5Fe^{3+} \rightarrow NAD^+ + Cytb_5Fe^{2+}$ (15)

$Cytb_5Fe^{2+} + HbFe^{3+} \rightarrow Cytb_5Fe^{3+} + HbFe^{2+}$ (16)

One molecule of cytochrome b5 can bind to one subunit of methemoglobin, mainly through lysine and/or arginine residues [27], and transfer the electron needed to reduce iron to the divalent state.

Another supplier of hydrogen is NADP, the main place of its formation is the pentose phosphate pathway of glucose metabolism. NADPH is reduced to NADPH, which itself reduces methemoglobin to hemoglobin under the action of another methemoglobin reductase, NADPH-flavin reductase, diaphorase II or NADPH-dehydrogenase [28, 29]:

NADPH- reductase

NADPH + flavin *(oxidized form)* $\rightarrow$ $NADP^+$ + dihydroflavin *(reduced form)* (22)

dihydroflavin + $Fe^{3+} \rightarrow$ flavin + Fe^{2+} (17).

In a non-enzymatic way, methemoglobin is reduced to hemoglobin as a result of the reaction with ascorbic acid or reduced glutathione (Table 1).

Ascorbic acid can penetrate the erythrocyte membrane and reduce the level of methemoglobin by transferring one electron

At the same time, ascorbic acid is oxidized to dehydroascorbic acid, which is then reduced by glutathione or directly by dehydroascorbate reductase [30, 31]:

So, the process of auto-oxidation of hemoglobin can be represented by the total equation:

$4\ (HbFe^{2+}\ O_2) + 2H^+ \rightarrow 4HbFe^{3+} + 2OH^- + 3O_2$ with formation $O_2^{-}{\cdot}$, $OH{\cdot}$, H_2O_2 (6)

Thus, gemoglobin (Hb) within red blood cells (RBC) is protected from oxidative processes by efficient enzymatic machineries such as cytochrome *b*5, or flavin, coupled with NADH-dependant or NADPH-dependent methemoglobin reductases, reduced glutathione (GSH) and small molecule reductants which include ascorbic acid and uric acid. Thus when small amounts of Hb are oxidized to ferric ($HbFe^{3+}$) and ferryl ($HbFe^{4+}$) forms, reduction to the oxygen carrying ferrous ($HbFe^{2+}O_2$) form occurs rapidly to restore oxygen carrying capability and prevent cellular injury which may be triggered by these oxidation intermediates (Fig. 3).Moreover, the RBC provides a functional protective barrier to excessive nitrosative agents such as endothelial-derived nitric oxide (NO) and peroxidative agents such as hydrogen peroxide (H_2O_2).

According to literature data, the physiological oxidation of hemoglobin is characterized by a certain sequence of autoxidation and oxidation reactions, as well as the presence of factors in erythrocytes and blood plasma that can reduce the level of methemoglobin or prevent its formation.

CONCLUSIONS

Thus, based on the above data, it can be concluded that in addition to the main, previously known functions of hemoglobin (gas transport, peroxidase, monooxygenase), it catalyzes a two-electron oxidase reaction in which O_2 is reduced to H_2O_2. The validity of this position is confirmed by experimental data on the formation of one of the products of "spontaneous autooxidation" of oxyhemoglobin - deoxyform - THIS is not oxidation of hemoglobin, iron remains +2 as well as the kinetic characteristics of this process in the range of pH 5.6 _8.9. It has been shown that the formation of hemoglobin complexes with low-molecular-weight compounds that are formed in the erythrocyte contributes to the preservation of its functional activity. This property acquires a special physiological significance in conditions of low pO2 values, when the probability of loss of the gas transport function of hemoglobin increases sharply, as a result of possible oxidation of the iron porphyrin structure.

The obtained results can be used for the objective assessment of oxygen binding properties of hemoglobin in patients with distress, destructive processes and intoxication.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Healthcare-associated infections after neurosurgical procedures in Ukraine: a multicentre study (2020-2022)

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ABSTRACT

Aim: To investigate the epidemiology, microbiology, and risk factors for healthcare-associated infections (HAIs) after a neurosurgical procedure in Ukraine.

Materials and Methods: Prospective multicentre surveillance was conducted from January 2020 to December 2022 in 10 regional hospitals of Ukraine. Definitions of HAIs were adapted from the Centers for Disease Control and Prevention's National Healthcare Safety Network.

Results: Of 8,623 neurosurgical patients, 1,579 (18.3%) HAIs were observed. The most frequently of HAI types were pneumonia (38.4%), surgical site infection (34.2%), urinary tract infection (18.1%) and bloodstream infection (9.3%). Death during hospitalization was reported in 11.3% of HAI cases. There was an association between HAIs after neurosurgical procedures and patients with diabetes mellitus, end-stage renal disease undergoing dialysis, and leukaemia. The strongest independent associations were observed for intubation, urinary catheters, and vascular catheters. Klebsiella pneumoniae were most commonly reported, accounting for 25.1% of all organisms, followed by Escherichia coli (17.6%), *Staphylococcus aureus* (9.9%), *Pseudomonas aeruginosa* (8.9%), *Acinetobacter baumannii* (8.5%), coagulase-negative staphylococci (6.8%), and Streptococcus spp. (5.5%). In total, 76.3% isolates from neurosurgical patients were MDROs. Antimicrobial resistance in Ukraine varies greatly by bacterial species, antimicrobial group, and region.

Conclusions: Healthcare-associated infections are a cause for mortality and morbidity among neurosurgical patients. This is due to increase emergence of antimicrobial-resistant pathogens. Routinely collected surveillance data are of great value as a basis for studying the consequences of HAIs.

KEY WORDS: Neurosurgery, healthcare-associated infection, prevalence, risk factors, mortality, antimicrobial resistance, Ukraine

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INTRODUCTION

Healthcare-associated infection (HAI) continues to be a significant problem, particularly after neurosurgery, where infection can result in rehospitalization, multiple operative procedures, and aggressive antibiotic therapy. HAIs after intracranial neurosurgery procedures remains a significant worldwide problem, resulting in substantial morbidity/mortality if not combatted quickly and energetically. These infections presented in the most dangerous and sometimes life-threatening forms of infection, such as pneumonia, bloodstream infection, and urinary tract infection. The prevention of these infections is correlated with high treatment costs and longer hospitalization times [1].

Most of these infections are caused by opportunistic organisms, such as gram-positive *Staphylococcus* species and *Enterococcus* spp., and gram-negative bacilli [2, 3]. Further, an increasing number of infections are caused by organisms that are resistant to multiple antibiotics [2, 3]. A few studies the use of the prophylactic antibiotics has been shown to significantly decrease the incidence of meningitis after neurosurgery, its effect on extra-neurosurgical-site infections has not been documented.

Understanding the incidence and pathophysiology of HAIs is the key to their prevention. Their impact on the patient's subjective well-being is always negative and significant, and their management requires considerable expenses for the health care systems. A previous study found that patients who developed a SSI were twice as likely to die, 1.6 times as likely to require intensive care treatment, and more than five times as likely to be readmitted to the hospital. As shown in a survey of healthcare associated infections (HAIs) by the European Centre for Disease Prevention and Control, SSIs were the second most common reason, accounting for 19.6% of all HAI between 2011 and 2012 [4].

In neurosurgery in general, large-scale studies reporting robust HAI estimates are currently lacking and a wide range of SSI rates between 1-8% for cranial procedures and 0.5-18.8% for spinal procedures have been reported [5-7]. Other study shown that pooled proportion of SSI was 10.4% when an immediate cranioplasty was done and 16.1% when delayed cranioplasty was done [8].

Although the danger of HAI is universally recognized, the reported incidence of HAIs after neurosurgery procedures remains variable. Today, in Ukraine there are only few reports on the incidence of HAIs in neurosurgery. We have previously reported HAI in Ukraine were ranging from 19.4% to 20.9% [3, 9, 10]. The impact of risk factors and adverse outcome on this reported variability has not been previously investigated.

AIM

The aim of the study was to investigate the epidemiology, microbiology, and risk factors for HAIs after a neurosurgical procedure in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING AND POPULATION

This multicentre prospective observational study was performed over a 36-month period (January, 2020 to December 2022) in 10 Ukrainian regional hospitals for adult patients, which are similar in terms of medical equipment, personnel, laboratory facilities. Within the structures of all hospitals, there are microbiological laboratories. These hospitals are not related administratively, and receive elective and emergency patients. Patients who were aged 18 years or older and underwent elective or emergency neurosurgical procedure, who stayed for more than 48 h in hospital, and survived at least 7 days after surgery were included in the study. Patients highly suspicious of central nervous infection prior to the procedure including subdural empyema, cerebral abscess, or infected pathological disease, and patients who passed away within 48 hours after the operation were excluded.

DEFINITION

In this study an HAI was defined as an infection arising >48 h after admission to hospital and not present or incubating on admission, unless the patient had been discharged from hospital within a defined period. The criteria for specific HAI site were adapted from the Centers for Disease Control and Prevention's (CDC) and National Healthcare Safety Network's (NHSN) case definitions. An incident HAI was defined by microbiologically confirmed CDC/NHSN HAI epidemiological case definitions. Institution of antimicrobial treatment by a physician was not considered to be sufficient for diagnosis of an HAI because of widespread use of empiric antimicrobial therapy in Ukrainian hospitals.

DATA COLLECTION

We developed a special questionnaire that collected data from medical records, including gender, age (years), discharges or deaths of patients, microbiological and radiographic investigations, invasive procedures, comorbidities, procedure/treatment, day of admission to the ICU, surgical interventions, previous hospitalization within one year after the current hospitalization, antibiotics usage, and culture and sensitivity of the clinical isolates. All participating hospitals had hospital infection control teams. The surveillance of HAIs in hospitals was based mainly on analysis of microbiological reports, databases on patients and telephone communication between the epidemiological nurse and the neurosurgery unit. The HAI monitoring in hospitals was an outcome of daily personal communication between the infection prevention and control nurse and patients in the neurosurgery unit and assessment of their health status based on clinical symptoms presented by the patient, epidemiological definitions by CDC/NHSN, microbiological and other diagnostic tests. Follow-up of each patient was continued for one month, and for some infections for up to 90 days.

ETHICS

Scientific workup of the data was approved by the institutional review board of the Shupyk National Healthcare University of Ukraine. The data used for the present analysis had been previously anonymized.

MICROBIOLOGICAL METHODS

In this study for the microbiological diagnosis of different HAI cases, appropriate clinical material (blood, swabs, urine samples and others) was collected following doctor's orders. Only the first isolate from each patient was selected for microbiological analysis, excluding subsequent cultures from the same patient and HAI case. Species identification was performed with standard microbial methods. Antibiotic susceptibility testing of bacteria was determined by Kirby-Bauer disc diffusion test according to the protocol of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://eucast.org). An isolate is considered resistant to an antimicrobial agent when tested and interpreted as R in accordance with the EUCAST clinical breakpoint criteria used by the local laboratory. When combining results

Table 1. Distribution of healthcare-associated infections (HAIs) after neurosurgical procedures in regional (tertiary care) hospitals, Ukraine, 2020-2022

Regional hospitals	Type of HAI								Total (n=1579)	
	PNEU (n=606)		SSI (n=540)		UTI (n=286)		BSI (n=147)			
	n	%	n	%	n	%	n	%	n	%
1	69	11.4	51	9.4	31	10.8	14	9.5	165	10.4
2	47	7.8	31	5.7	15	5.2	9	6.1	102	6.5
3	38	6.3	58	10.7	28	9.8	19	12.9	143	9.1
4	29	4.8	36	6.7	24	8.4	12	8.2	101	6.4
5	38	6.3	27	5.0	18	6.3	11	7.5	94	6.0
6	68	11.2	52	9.6	27	9.4	14	9.5	161	10.2
7	31	5.1	44	8.1	31	10.8	18	12.2	124	7.9
8	34	5.6	33	6.1	22	7.7	17	11.6	106	6.7
9	126	20.8	106	19.6	59	20.6	21	14.3	312	19.8
10	126	20.8	102	18.9	31	10.8	12	14.3	271	17.2

HAI, healthcare-associated infection; PNEU, pneumonia; SSI, surgical site infection; UTI, urinary tract infection; BSI, bloodstream infection.

Table 2. Trend of the most frequently recorded types of healthcare-associated infections (HAIs) after neurosurgical procedures in regional (tertiary care) hospitals, Ukraine, 2020-2022

Type of HAI	2020	2021	2022	Total (2020-2022)		Trend 2020-2022
	%	%	%	No. (%)	95% CI	
Pneumonia	36.8	37.1	37.7	606 (38.4)	37.2-39.6	↑
Surgical site infection	33.7	33.9	34.6	540 (34.2)	33.0-35.4	↑
Urinary tract infection	18.1	18.9	18.9	286 (18.1)	17.1-19.1	↑
Bloodstream infection	11.4	10.1	8.8	147 (9.3)	8.6-10.0	↓

for antimicrobial agents representing an antimicrobial group, the outcome is based on the most resistant result.

STATISTICAL ANALYSIS

In this study IBM SPSS (SPSS-Statistical Package for the Social Sciences, STATISTICS 24, Armonk, NY, USA) and Microsoft Excel were used in the statistical analysis of the collected material. Statistical analysis presents descriptive statistics for the characteristics of patients, and types of HAI.

The analysis of differences between the analyzed departments was performed using Pearson's chi-square. Univariate and multivariate analyses were conducted with SPSS 16 software. Logistic regression allowed for the estimation of the effect size of certain predictors of HAI. The level of significance was $p < 0.05$.

RESULTS

PREVALENCE OF HAI

In the surveillance period, a total of 8623 neurosurgical procedures were performed in hospitalized patients. In this cohort, we detected 1579 healthcare-associated infections (HAIs), but in each hospital, the rates were different (Table 1). Of the total HAI cases, 14.8% were detected after hospital discharge. The prevalence of HAI among patients after neurosurgical procedures in Ukrainian hospitals was 18.3% (95% CI: 17.9-18.7). The most frequently recorded types of HAIs were: pneumonia (PNEU), 38.4% (95% CI:37.2-39.6); surgical site infection (SSI), 34.2% (33.0-35.4); urinary tract infection (UTI), 18.1% (95% CI:17.1-19.1); and bloodstream infection (BSI), 9.3% (95% CI:8.6-10.0). Of all HAIs, 9.4% (PNEU) were defined as part of an outbreak. The most frequent specific types of HAI among operated patients are reported in Table 1. There was an increase in the rate of HAI during the study period ($P < 0.0001$), largely associated with increased rates of PNEU, SSI, UTI, SSI, and BSI (Table 2). The prevalence of HAI among patients after neurosurgical procedures varied widely within Ukraine, from <10% in two (20.0%) of 10 regional hospitals to ≥15% in eight (80.0%), mostly in southern, eastern, and central Ukraine. An increase in the incidence of HAI was observed in 8 (80.0%) out of 10 regional hospitals, mostly in southern, eastern, and central Ukraine.

RISK FACTORS FOR HAI

An overview of the analysed patient characteristics and risk factors for HAI are shown in Table 3. The risk factors in

Table 3. Patient characteristics and risk factors for healthcare-associated infection (HAI) after neurosurgical procedures in regional (tertiary care) hospitals, Ukraine, 2020-2022

Variables	HAI				P value
	No		Yes		
	n	%	n	%	
All	7,044	81.7	1,579	18.3	0.05
Gender					0.49
Male	4,543	64.5	1,080	68.4	
Female	2,501	35.5	499	31.6	
Age (years)					0.001
18-34	339	6.9	76	4.8	
35-44	444	8.4	100	6.3	
45-54	275	9.4	62	3.9	
55-64	698	22.8	156	9.9	
65-74	1,142	19.6	256	16.2	
75-84	1,909	16.5	428	27.1	
≥85	2,237	16.3	501	31.8	
Admission type					0.083
Emergency or Urgent	4,162	59.1	687	43.5	
Elective	2,882	40.9	892	56.5	
Length of stay in ICU >5 (days)	7,366	31.8	1,257	77.6	<0.001
McCabe score					<0.001
Non-fatal	2,590	36.8	134	8.5	
Ultimately fatal	2,431	34.5	299	18.9	
Rapidly fatal	1,230	17.4	529	33.5	
Missing	793	11.3	617	39.1	
Duration of operative procedure (hrs)					0.034
≤4	4,673	66.3	532	33.7	
>4	2,371	33.7	1,047	66.3	
Comorbidities					
Diabetes mellitus	1,067	15.1	499	31.6	0.009
End-stage renal disease with dialysis	766	10.9	354	22.4	0.009
Peripheral vascular disease	2,056	29.2	0	0.0	0.24
Cerebrovascular accident	588	8.3	103	6.5	0.31
Peptic ulcer disease	483	6.9	84	5.3	0.85
Myocardial infarction	569	8.1	82	5.2	0.91
Congestive cardiac failure	501	7.1	84	5.3	0.43
Liver disease	357	5.1	61	3.9	0.42
Leukaemia	647	9.3	312	19.8	0.009
Procedure/treatment					
Mechanical ventilation	5,148	73.1	1,558	98.7	<0.001
Central venous catheter	4,638	65.8	1,204	76.3	0.05
Peripheral vascular catheter	4,552	64.6	1,132	71.7	0.19
Urinary catheter	4,321	61.3	1,455	92.1	<0.001
Transfusion	2,074	29.4	728	46.1	0.02
Sedation	5,641	80.1	1,449	91.8	0.02

HAI, healthcare-associated infection; ICU, intensive care unit.

Table 4. Distribution of pathogens (n=3872) isolated from neurosurgical patients (n=1579) with healthcare infections (HAIs) in Ukraine (2020-2022)

Types of micro-organisms	Type of HAI								Total no. (%) of isolates	95% CI
	PNEU		SSI		UTI		BSI			
	n	%	n	%	n	%	n	%		
Gram-positive cocci	203	19.9	274	26.8	308	30.1	237	23.2	1022 (26.4)	25.7 – 27.1
Staphylococcus aureus	82	21.5	147	38.5	56	14.7	97	25.4	382 (9.9)	9.4 – 10.4
CoNS	17	6.4	74	27.9	91	34.3	83	31.3	265 (6.8)	6.4 – 7.2
Staphylococcus haemolyticus	9	15.5	14	24.1	17	29.3	18	31.0	58 (1.5)	1.3 – 1.7
Streptococcus spp.	84	39.4	12	5.6	95	44.6	22	10.3	213 (5.5)	5.1 – 5.9
Enterococcus spp.	11	10.6	27	26.0	49	47.1	17	16.3	104 (2.6)	2.3 – 2.9
Gram-negative bacilli	755	27.4	699	25.4	926	33.6	362	13.2	2752 (71.1)	70.4 – 71.8
Klebsiella pneumoniae	406	41.7	97	10.0	344	35.4	126	12.9	973 (25.1)	24.4 – 25.8
Escherichia coli	46	6.8	254	37.5	297	43.8	81	11.9	678 (17.5)	16.9 – 18.1
Serratia marcescens	21	20.4	41	39.8	18	17.5	23	22.3	103 (2.7)	2.4 – 3.0
Proteus mirabilis	7	7.2	10	10.3	74	76.3	6	6.2	97 (2.5)	2.3 – 2.7
Enterobacter aerogenes	8	14.3	15	26.8	27	48.2	6	10.7	56 (1.4)	1.2 – 1.6
Enterobacter cloacae	7	8.5	28	34.1	29	35.4	18	22.0	82 (2.1)	1.9 – 2.3
Stenotrophomonas maltophilia	14	22.2	24	38.1	8	12.7	17	27.0	63 (1.6)	1.4 – 1.8
Pseudomonas aeruginosa	68	20.4	173	50.3	84	24.4	9	2.6	334 (8.9)	8.4 – 9.4
Acinetobacter baumannii	175	53.4	48	14.6	31	9.5	74	22.6	328 (8.5)	8.1 – 8.9
Other gram-negative bacteria	3	10.7	9	32.1	14	50.0	2	7.1	28 (0.7)	0.6 – 0.8
Fungi	15	15.3	9	9.2	50	51.0	24	24.5	98 (2.5)	2.3 – 2.7
Candida albicans	12	14.8	8	9.9	42	51.9	19	23.5	81(2.1)	1.9 – 2.3
Nonalbicans fungi	3	17.6	1	5.9	8	47.1	5	29.4	17 (0.4)	0.3 – 0.5

HAI, healthcare infection; PNEU, pneumonia; SSI, surgical site infection; UTI, urinary tract infection; BSIs, bloodstream infections; CoNS, coagulase-negative staphylococci; CI, confidence interval.

this study were significantly associated with the prevalence of HAI. By including the risk factors with $P < 0.05$ from the univariate analysis (Table 3) in a forward logistic regression analysis, the independent risk factors for HAI were obtained. There was an association between the prevalence of HAIs after neurosurgical procedures and patients with diabetes mellitus, end-stage renal disease undergoing dialysis, and leukaemia. The HAI incidence was highest among patients admitted to ICU, where 37.5% of patients had at least one HAI. In this study, patients with end-stage renal disease undergoing dialysis, and those with an ICU stay of more than five days were associated with a higher risk of contracting an HAI. The strongest independent associations were observed for intubation, urinary catheters, and vascular catheters (before the onset of pneumonia, UTI, and BSI, respectively). The prevalence of HAI increased with age. Most cases of pneumonia and UTI were device-associated, and cases of BSI were central-line-associated (Table 3).

INPATIENT MORTALITY FROM HAI

Of the cases of HAI identified, 14.7% died before discharge. Mortality patients with HAI increased with age for both sexes. The highest mortality risk was observed in patients with pneumonia and in patients with BSI. The highest mortality was observed in patients with PNEU (77.3%), followed by those with BSI (22.7%). In this study there were no deaths in patients with UTI and SSI. A high McCabe score was also associated with increased inpatient mortality.

PATHOGENS AND ANTIMICROBIAL RESISTANCE

In total, 3872 pathogens (Gram-negative and -positive bacteria) were isolated from 1579 neurosurgical patients with HAI. A general analysis of etiological agents of HAI showed that the most frequently isolated bacteria were *Klebsiella pneumoniae* (25.1%), followed by *Escherichia coli* (17.6%), *Staphylococcus aureus* (9.9%), *Pseudomonas aeruginosa* (8.9%), *Acinetobacter baumannii* (8.5%), coagulase-negative staphylococci (6.8%), and *Streptococcus* spp. (5.5%). A polymicrobial infection was seen in 59% of the HAI cases. PNEU were most commonly caused by *Acinetobacter* spp. (53.4%), *K. pneumoniae* (41.7%), *Streptococcus* spp. (39.4%), *Ste-*

notrophomonas maltophilia (22.2%), *S. aureus* (21.5%), and *Serratia marcescens* (20.4%). In BSI, the dominant etiological agents were CoNS (31.3%), *Staphylococcus haemolyticus* (31%), *S. maltophilia* (27%), *S. aureus* (25.4%), *Candida albicans* (23.5%), *A. baumannii* (22.6%), and *S. marcescens* (22.3%). For UTI, the agents were *C. albicans* (51.9%), *Enterobacter aerogenes* (48.2%), *Enterococcus* spp. (47.1%), *Streptococcu*s spp. (44.6%), and *E. coli* (43.8%). In SSI, the most frequently isolated microorganism was *P. aeruginosa* (50.3%), *S. marcescens* (39.8%), *S. aureus* (38.5%), *S. maltophilia* (38.1%), and *E. coli* (37.5%), *E. aerogenes* (26.8%), and *Enterococcus* spp. (26%) (Table 4).

In total, 76.3% isolates from neurosurgical patients were MDROs. Most of the HAI cases were observed in patients caused by MDR strains of *K. pneumoniae* (31.9%), *A. baumannii* (31.4%), P. aeruginosa (14.3%), *S. maltophilia* (13.8), *S. aureus* (12.9%), followed by *E. coli* (9.2%), *Enterobacter* spp. (8.9%), *Enterococcus* spp. (8.7%), and *S. marcescens* (7.1%). This study showed that antimicrobial resistance in Ukrainian hospitals varies greatly by bacterial species, antimicrobial group, and region. For several bacterial species-antimicrobial group combinations, significant differences are evident. In general, lower resistance percentages were reported by Ukrainian regions in the west while higher percentages were reported in the north, south, and east of Ukraine.

DISCUSSION

The results presented in this study are based on multicentre prospective surveillance data for HAI after neurosurgical procedure in Ukraine. This study expands upon the previous reports and is the first multicentre prospective study to publish prevalence of HAI types, risk factors for HAI, inpatient mortality from HAI, and frequent pathogens and antimicrobial resistance of responsible pathogens of HAI in neurosurgical patients in Ukraine [9,10].

This survey identified a high prevalence of HAI (18.3%) and high mortality for neurosurgical patients with HAI (14.7%). A previous study in Ukraine conducted in 2021 found that prevalence of HAI and mortality rate in neurosurgical patients were 20.9% and 11.3%, respectively [10]. In other countries prevalence of HAI in neurosurgical patients was from 3.1% to 9.1% [2, 11] and mortality was from 3.5% to 12% [12-15]. The prevalence of HAI among neurosurgical patients varied widely within Ukraine. An increase in the incidence of HAI was observed in 67.4% of regional hospitals.

In the present study the most frequent specific types of HAI in neurosurgical patients were PNEU, SSI, UTI, and BSI. Our results are consistent with those of previous studies in other countries [2,10, 11]. There was an increase in the rate of HAI among neurosurgical patients in study period, largely associated with increased rates of PNEU, SSI, and UTI (Table 2).

In this study, *K. pneumoniae, E. coli, S. aureus, P. aeruginosa, A. baumannii,* CoNS, and *Streptococcus* spp. were common HAI pathogens in neurosurgical patients. In general, the pathogens associated with HAI varied by location (PNEU, SSI, UTI, and BSI). Our study showed that the situation with antimicrobial resistance in Ukraine varies greatly by bacterial species, antimicrobial group, and region. In total, 76.3% isolates from neurosurgical patients with HAI were MDROs. Most of the HAI cases were observed in patients caused by MDR strains of *K. pneumoniae, A. baumannii*, *P. aeruginosa, S. maltophilia, S. aureus,* followed by *E. coli, Enterobacter* spp., *Enterococcus* spp., and *S. marcescens.* Our study showed that mortality among neurosurgical patients was higher among patients with HAI caused by MDROs. A previous study in Ukraine conducted in 2020-2021 found that 85.1% isolates from patients in regional hospitals were MDROs. The majority of MDRO isolates carried b-lactamase genes. [3]. In Ukrainian regional hospitals, resistance to third-generation cephalosporins and carbapenems generally was higher in *K. pneumoniae* than *E. coli*. While carbapenem resistance remained <10% for *E. coli* in most regions of Ukraine, 30% of hospitals reported *K. pneumoniae* resistance rates of >40% [3]. The proportions of MDROs among isolates from patients with HAIs, environmental surfaces and HCWs (hands, gown/gloves) were 29.2%, 16.3% and 24.2%, respectively. In 51.9% of the tested isolates, identical MDROs were found in clinical isolates, environmental samples and HCWs' hands [16].

The risk factors in present study were significantly associated with the prevalence of HAI. There was an association between the prevalence of HAIs after neurosurgical procedures and patients with diabetes mellitus, end-stage renal disease undergoing dialysis, and leukaemia. In our study the strongest independent associations were observed for intubation, urinary catheters, and vascular catheters (before the onset of pneumonia, UTI, and BSI, respectively). The prevalence of HAI increased with age. Most cases of PNEU and UTI were device-associated, and cases of BSI were central-line-associated. Results our study are consistent with those of previous studies in other countries [17-22].

STRENGTH AND LIMITATION

Strength of this study was that it was a prospective multi-centre observational cohort study, based on HAI surveillance data in neurosurgical patients and

using CDC/NHSN methodology. Our study has some limitations. The study was based on a strict CDC/NHSN protocol comprising the definitions and criteria of HAIs. There was no validation of the process in the hospitals under study and no power analysis was performed when planning this study.

CONCLUSIONS

Healthcare-associated infections are a cause for high morbidity and mortality among neurosurgical patients. This is due to increase emergence of antimicrobial-resistant pathogens. The patients in the neurosurgical ward are exposed to many risk factors causing HAIs. These factors are related to operations, invasive diagnosing and monitoring of the nervous system and mechanical support of vital functions. HAIs in neurosurgical patients remain a challenge for diagnosis, treatment, and prevention. The high prevalence and resistant profile of HAIs has important implications for patient safety and emphasizes the need to strengthen collaboration between infection control teams to prevent serious complications in this setting. Routinely collected surveillance data are of great value as a basis for studying the consequences of HAIs. Gaining a better understanding of at-risk patients and development of preventative strategies will be the goal for future investigation.

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ORIGINAL ARTICLE

CONTENTS

Pregravid preparation of women with chronic endometritis in IVF cycles

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ABSTRACT

Aim: of our study was to improve the pregravid preparation of women with chronic endometritis to develop individual approaches to overcoming infertility, taking into account the state of endometrium.

Materials and Methods: The study included 90 women (main group, n=90), 28 to 38 years with an anatomically normal uterus and chronic endometritis (CE). Patients were divided into 2 groups: group I – 45 women with CE who received conventional treatment; group II – 45 women with CE who received pregravid preparation by subendometrial injections of Platelet-Rich Plasma (PRP).

Results: At the first stage of study, the ART statistical reports from 2015 to 2022 were analyzed at the Medical Center of Reproductive Health «Damia», (Ivano-Frankivsk). Analysis of the vaginal flora parameters before treatment at the first stage revealed the presence of conditionally pathogenic flora in culture from the cervical canal (*Candida albicans* – 2.4%, *Escherihia coli* – 4.8%, *Staphylococcus epidermidis* – 6.2% *Enterococcus faecalis* – 6.9%), and was evidence of a possible recurrence of inflammation during gestation. In the age category, the groups of patients were homogeneous, with no significant differences by the level of AMH and the level of CD 138. Biochemical pregnancy be present in 20 patients (44.4%) of group I and 28 (62.2%) of group II. Fertility within a year after the end of therapy was restored with the proposed method of therapy in most women (51.1%), in the comparison group this number was 11.1% lower. Pregnancy rate between the groups (I and II) did not differ significantly. The number of live births in group II — 19 births (42.2%) — was 2 times higher than I group (9 (20.0%), P<0.05). The most common complication for women in the comparison groups was early pregnancy loss. Among 18 (40.0%) clinical pregnancies of group I, 8 women (17.8%) had early miscarriage, 1 ectopic pregnancy (2.2%), while in group II clinical pregnancy be present in 23 women (51.1%). The number of terminated pregnancies was two times lower than in the first group (8.9% vs. 17.8%, P<0.05).

Conclusions: Chronic endometritis is one of the main causes of pregnancy loss after in vitro fertilization. Patients of the second group were treated with the proposed method of subendometrial injections with Platelet-Rich Plasma (PRP), prepared from autologous blood, is an effective method of preparing the endometrium for embryo transfer and can increase the number of live births in patients with chronic endometritis.

KEY WORDS: chronic endometritis, Platelet-Rich Plasma, miscarriage, CD 138

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INTRODUCTION

Infertility, miscarriage, especially in the early stages, have a leading place in the causes of low birth rates associated with medical problems. The frequency of this pathology does not tend to decrease and, conversely, during wartime it becomes not only a medical, but also a global social problem of Ukraine [1].

One of the main tasks of the Health Service of Ukraine during the war and economic problems is to preserve every desired pregnancy and the birth of a healthy child. In 2023, the number of pregnancies decreased by 2 times. Infertility, miscarriage, especially in the early stages, have a leading place in the causes of low fertility associated with medical problems. The frequency of this pathology does not tend to decrease, and conversely, during wartime, the divorces of young couples, military losses of young men of reproductive age, forced emigration of young women abroad, the problem of preserving each pregnancy and creating conditions for its development becomes not only a medical but also a global social problem of Ukraine.

Health of the maternal organism and uterine cavity itself, — the site of the first meeting of the embryo and pregravid endometrium, is extremely important for the normal development of gestational sac. Today, chronic endometritis (CE) is one of the leading causes of unsuccessful ART, the causes of silent miscarriage in the early stages [2].

According to world studies [2, 3, 4], CE is the result of bacterial-viral contamination of the endometrium

and loss of the ability of local immunity and specific and nonspecific defenses of the woman's body to resist pathogens. The last decades are characterized not only a change of genital infection pathogens (viral infection and opportunistic microflora took the first place), but also a change in the clinic of inflammatory processes (primary latent course without clinical manifestations) [5]. Treatment of infertility in patients with chronic endometritis is accompanied by disorders of the morphofunctional state of the endometrium, which requires the development of minimally invasive diagnostic methods and an individualized treatment method for pregravid preparation of the endometrium for embryo transfer, a means to increase the live births in this category of patients.

In reproductive medicine, there are known facts about the effect of Platelet-Rich Plasma (PRP) on endometrial proliferation. The effectiveness of PRP therapy for endometrial proliferation in chronic endometritis remains very interesting. The question of the effectiveness of PRP therapy for endometrial proliferation in chronic endometritis remains very interesting [1, 5, 6, 7].

Due to platelet activation in PRP, growth factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and cytokines become biologically active and are secreted within 10 minutes of clotting [8, 9, 10, 11].

All of the above biologically active substances stimulate the growth and transformation of endometrial cells, participate in tissue regeneration; in the regulatory cell migration, reconstruction of the extracellular matrix; in cell proliferation and cell differentiation; in angiogenesis [6, 8, 9, 12, 13].

Since PRPs are derived from autologous blood, is minimized the risk of disease transmission, immunogenic reactions. Platelet-Rich Plasma has already become widespread in ophthalmology, orthopedics and surgery for wound healing [1, 4, 7, 11, 12, 14, 15].

AIM

The aim of our study was to improve the pregravid preparation of women with chronic endometritis to develop individual approaches to overcoming infertility, taking into account the state of endometrium.

MATERIALS AND METHODS

The study included 90 women (main group, n = 90), 28 to 38 years with an anatomically normal uterus and chronic endometritis (CE). Diagnostic criteria for CE in infertility women were a hysteroscopic picture of endometrial micropolips, local or diffuse endometrial hyperemia, «strawberry symptom» [4] and expression of the CD 138 proliferation marker according to the results of an immunohistochemical study of endometrial biopsy.

Patients were divided into 2 groups: group I – 45 women with CE who received conventional treatment; group II – 45 women with CE who received the proposed treatment. The patients of the second group were treated with the proposed method of administering Platelet-Rich Plasma (PRP) by subendometrial injections using a Kitazato OPU needle 325 mm through the operating channel of the Bettocchi 5 mm hysteroscope in first half of the proliferative phase of the cycle (4–6 injections). Platelet-Rich Plasma was prepared from autologous blood. Blood was drawn from the peripheral vein into an anticoagulant tube and processed by separating different blood components by a modified two-stage centrifugation method [3]. Patients of the second group were familiarized with the treatment method and signed a voluntary informed consent to the procedure.

The control group consist of 25 healthy women at the preparation for motherhood with a male factor of infertility.

Statistical analysis was performed using Statistica 10.0.

RESULTS AND DISCUSSION

At the first stage of the study, the ART statistical reports from 2015 to 2022 were analyzed at the Medical Center of Reproductive Health «Damia», (Ivano-Frankivsk). 600 cycles in women who underwent artificial insemination in vitro were analyzed. The main group of women who had confirmed chronic endometritis was identified.

All patients of the main group underwent antibacterial treatment to correct the microbial biotope of the vagina, depending on the identified pathogens. As antibacterial therapy, classical schemes of combination of broad-spectrum antibiotics with metronidazole and (or) clindamycin with presence of an anaerobic component were used.

Analysis of the vaginal flora before treatment at the first stage revealed the presence of conditionally pathogenic flora in culture from the cervical canal (*Candida albisans – 2.4%, Escherihia coli – 4.8%, Staphylococcus epidermidis – 6.2% Enterococcus faecalis – 6.9%),* and was evidence of a possible recurrence of inflammation during gestation. Conventional treatments have been shown to effect. In the endometrial aspirates from women of the main group, the pathogens was not found, which indicates a good effect of the proposed preventive and therapeutic method.

Table 1. Clinical results of in vitro fertilization in women with chronic endometritis after embryo transfer depending on the pregravid preparation of the endometrium

Group	Clinical pregnancy		Live birth		Miscarriage		Ectopic pregnancy	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Group I (n=45)	18	40.0	9	20.0*	8	17.8*	1	2.2
Group II (n=45)	23	51.1	19	42.2	4	8.9	0	0
Control group (n=25)	25	100	24	96.0	5	20.0	1	4.0

Note: * - P<0.05 – the significance of differences between indicators of groups I and II

Pregravid preparation of the second group patients began in the absence of sexually transmitted infections, and included, besides the traditional use of folates, PRP therapy by subendometrial injections for the immunomodulatory, antiviral action and blocking production of anti-inflammatory cytokines.

Patient reproductive history questionnaires were evaluated prior to pregravid preparation.

The groups of patients were homogeneous in the age category, with no significant differences by the levels of AMH and CD138. Biochemical pregnancy occurred in 20 patients (44.4%) of group I and 28 (62.2%) of group II. Embryo transfer was performed, respectively, one cycle after subendometrial injections with Platelet-Rich Plasma (PRP) in a standard endometrial preparation protocol prior to transfer of cryopreserved embryos: transdermal estradiol at 1 g per day from Day 5 of the cycle, ultrasound was performed from Day 10 to Day 13, if the endometrium reached a size of ≥7 mm, 250 μg chorion gonadotropin alfa was administered once. Micronized progesterone 800 mg from the next day. On the day of administration of chorion gonadotropin alfa and day of embryo transfer, the blood progesterone level was measured. 5-day-old good quality embryos by a morphological scale were transferred into the uterine cavity. All hormone therapy was administered before the day of the pregnancy test, i.e. 2 weeks from the date of embryo transfer until fetal imaging.

The reproductive results in patients with CE were evaluated depending on the method of pregravid preparation of the endometrium before thawed embryos transfer (Table 1).

Analyzing the data, it can be noted that fertility within a year after the end of therapy was restored with the proposed method of therapy in most women (51.1%), in the comparison group this number was 11.1% lower. Pregnancy rate between the groups (I and II) did not differ significantly.

The number of live births in group II — 19 (42.2%) — was 2 times higher than I group (9 (20.0%), P<0.05). The increase in the absolute benefit (therapeutic benefit) of the proposed method of pregravid preparation was 22.2% (95% CI 5.16-46.35%).

The most common complication for women in the comparison groups was early pregnancy loss. Among 18 (40.0%) clinical pregnancies of group I, 8 women (17.8%) had early miscarriage, 1 ectopic pregnancy (2.2%), while in group II clinical pregnancy be present in 23 women (51.1%). The number of terminated pregnancies was two times lower than in the first group (8.9% vs. 17.8%, P<0.05).

CONCLUSIONS

Chronic endometritis is one of the main causes of pregnancy loss after in vitro fertilization. Patients of the second group were treated with the proposed method of subendometrial injections with Platelet-Rich Plasma (PRP), prepared from autologous blood. This is an effective method of preparing the endometrium for embryo transfer and can increase the number of live births in patients with chronic endometritis.

The data indicate the effectiveness of the proposed improved algorithm for pregravid preparation of women with chronic endometritis in ART cycles.

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ORIGINAL ARTICLE

CONTENTS

International classification of functioning, disability and health with long-term consequences of cranio-brain injury

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ABSTRACT

Aim: To describe health status and related functioning of patients with different severity of traumatic brain injury (TBI) in past medical history in Ukraine and determining the feasibility of using the International Classification of Functioning, Disability and Health (ICF) Brief Core Set for TBI.

Materials and Methods: A total of 102 patients, who were treated in the neurological department of Dnipropetrovsk regional clinical hospital and State Institution «Ukrainian State Scientific Research Institute of Medical and Social Problems of Disability of Health Ministry of Ukraine», had been examined. Patients were divided into three groups: mild, moderate and severe TBI in past history and evaluated using ICF Brief Core Set for TBI.

Results: The most common problems in the functioning and health of patients in remote period of TBI, along with the influencing factors have been identified in the study. The most frequent categories from «Body Functions» and «Activity and Participation» sections in which patients had alterations were: memory functions, emotional functions, sensation of pain, functions of attention, brain structure, complex interpersonal interactions, family relationships. The increase in the amount and severity of disturbances with increasing severity of TBI had been established in all categories, except complex interpersonal interactions and family relationships.

Conclusions: Patients of all groups identified the family and close relatives, healthcare service and social welfare services, as the most frequent relieving factors of life activity. The use of the ICF Brief Core Set for assessing the subjects with TBI in past history provides a convenient procedure to standardize and structure functioning description. Information collected by the ICF Brief Core Set may be used for different purposes: clinical assessment, administration of medical services, planning and implementation of rehabilitation and evaluation of results, in scientific research, reports and health care statistics.

KEY WORDS: disability, remote consequences of traumatic brain injury, International Classification of Functioning, Disability and Health

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INTRODUCTION

Traumatic brain injury (TBI) is an important medical and social problem which is recognized as a global health priority. Life expectancy of patients with TBI in past history is lower than that of the age- and sex-matched general population: 20-year-old women who walked well represented a reduction of 6,9 years from the normal general population figure; for 20-year-old men who walked well the figure represented a reduction of 8,1 years from normal [1].

Spectrum of disorders, faced by the patients after craniocerebral trauma, is very wide: from headaches and nausea to an overall reduction in quality of life and social functioning. It determines the complexity and diversity of rehabilitation interventions in this patients' category. The concept of quality and success of rehabilitation has also evolved from simple recovery of functions regeneration and absence of complications, to the possibility of reintegration into society and restoration of the initial level of participation in all social processes. The instruments of patient's condition estimation have been changed too. Current methods' purposes are the broad analysis of not only physical, but also social and professional components of the patient's life [2]. It has critical importance during setting of aims for rehabilitation and identification of unmet rehabilitation needs of individuals with disability [3, 4]. The International Classification of Functioning (ICF) is such an instrument. It covers the whole range of health indicators and related domains in more than 1400 categories. The usability requirement the ICF has led to the development of ICF sets for different patients' groups.

AIM

The aim of this study is to describe health status and related functioning of patients with different severity of

TBI in past medical history in Ukraine and determining the feasibility of using the ICF Brief Core Set for TBI.

MATERIALS AND METHODS

We examined a total of 102 patients treated in neurological departments of Dnipropetrovsk regional clinical hospital and State Institution «Ukrainian State Scientific Research Institute of Medical and Social Problems of Disability of Health Ministry of Ukraine». The inclusion criteria in the study were: 1) diagnosis of TBI in the past history, confirmed by medical records; 2) age older than 18 years; 3) absence of concomitant severe disease; 4) informed consent signed by the individual with TBI. The criteria for exclusion from our study were: 1) stroke, encephalitis, meningitis, or other significant neurological disease in past medical history; 2) clinically significant abnormalities, illness or disorder of any body or organ system influencing central nervous system; 3) history of drug abuse, or excessive alcohol beverage consumption. The patients were divided into three groups: 1stgroup – 34 (32,0%) patients (6 (12,5%) females and 28 (87,5%) males; age – 39,8±8,8 years) with mild TBI; 2ndgroup –35 (35,0%) patients (2 (5,7%) females and 33 (94,3%) males; age – 39,09±7,03 years) with moderate TBI; 3rd group – 33 (33,0%) patients (100% males; age – 40,2±10,9 years) with severe TBI. This gender distribution corresponds with the data presented in modern articles, indicating higher prevalence of injury among men.

ICF Brief Core Set for TBI was used to describe the health status and related functioning of patients. It includes: 8 categories of body functions (labeled with the letter "b"), 1 category of body structure (labeled with the letter "s"), 8 categories of activity and participation (labeled as "d") and 6 categories of environmental factors (labeled with the letter "e"). Categories of «Body Functions», «Body Structures» and «Activities and Participation» sections comprise health condition. «Environmental and Personal Factors» section form a group of contextual factors. Changes in one component influences one or more of the other components, thus making bidirectional interaction between the factors. At least one specificator is used to provide information regarding the status of this function for five-level grades after the main code: 0: no problem; 1: minor problem; 2: moderate problem; 3: severe problem, 4: complete problem. Environmental factors are evaluated as being facilitating (graded from +1 to +4) or barrier (grade 1 to 4). Facilitators improve or even eliminate a disability, while barriers produce or increase the severity of a disability.

Data was collected through analysis of all available medical records, direct observation, neurological examination and questionnaire administration. The following instruments were also used to evaluate the categories of the ICF Brief Core Set for TBI: motion assessment by Goff, Barthel index, the Montreal Cognitive Assessment, the Frontal Assessment Battery, «10 words» Luria test, Schulte tables, SF36v2 health survey and Beck scale. Additionally, data of computed tomography of the brain were used during assessment of category s110 brain structure.

Statistical analysis was performed in Statistica 10.0, using frequency tables in descriptive statistics.

RESULTS

Across all categories of the ICF Brief Core Set for TBI, the presence of disturbances of varying severity and incidence, depending on the severity of craniocerebral trauma in the past, was established. Increasing severity of TBI was associated with the enlargement of the quantity and gravity of issues identified by the most of categories in ICF Brief Core Set.

Almost all the problems of the studied patients' groups were reflected in the categories of this set. The exceptions were revealed in two patients. They had hyperkinesis, impaired vision and hearing. These categories are not represented in the ICF Brief Core Set for TBI.

According to the results of our study, most of the disturbances were identified within sections «Body Functions» and «Body Structures», and to a lesser extent in section «Activity and Participation». The results of previous studies on this topic differ between each other, but at the same time the majority of studies prove the prevalence of disturbances within «Activity and Participation» and «Body Functions» sections [5, 6].

The most frequent categories in which patients had alterations were: memory functions, emotional functions, sensation of pain, functions of attention, brain structure, complex interpersonal interactions, and family relationships. Figure 1 presents the following ICF categories: b164 high-level cognitive functions, b152 emotional functions, b130 energy and motor functions, b760 control of voluntary movements, b144 memory functions, b280 pain sensation, b140 attention functions, b110 consciousness functions, s110 brain structure, d230 doing daily activities d350 talking, d450 walking, d720 complex interpersonal interactions, d845 acquiring, keeping and quitting jobs, d5 personal care, d920 rest and leisure d760 family relationships.

In the categories relating to the body functions, in addition to the mentioned above, a significant proportion of patients also had problems (the sum of qualifiers 1-4) with high-level cognitive functions and energy and drive functions.

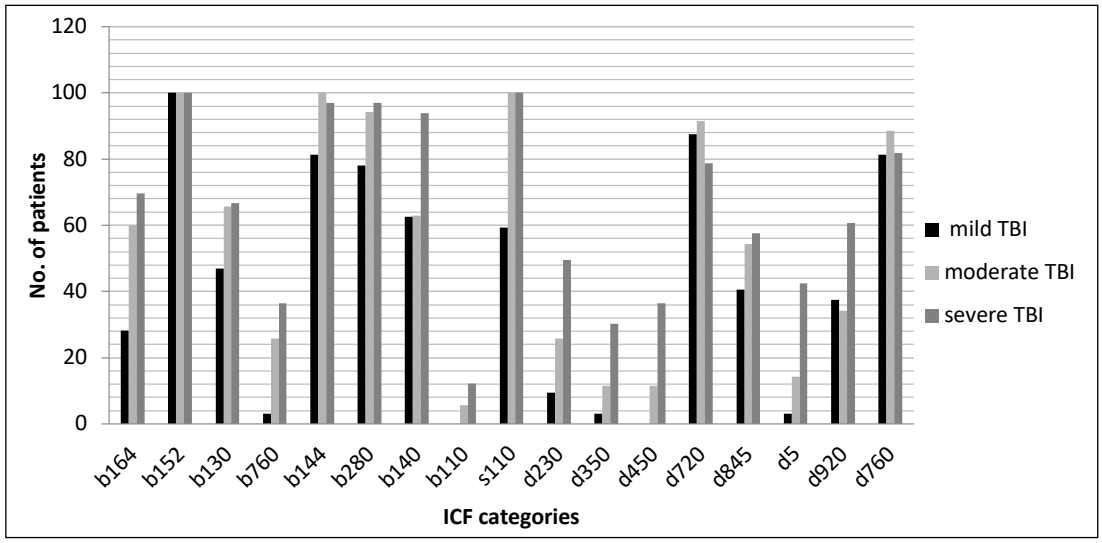

Fig 1. The proportion of patients (%) with identified disturbancesin the following sections: «Body Functions»(b), «Body Structures» (s), and «Activity and Participation» (d) ICF Brief Core Set for TBI

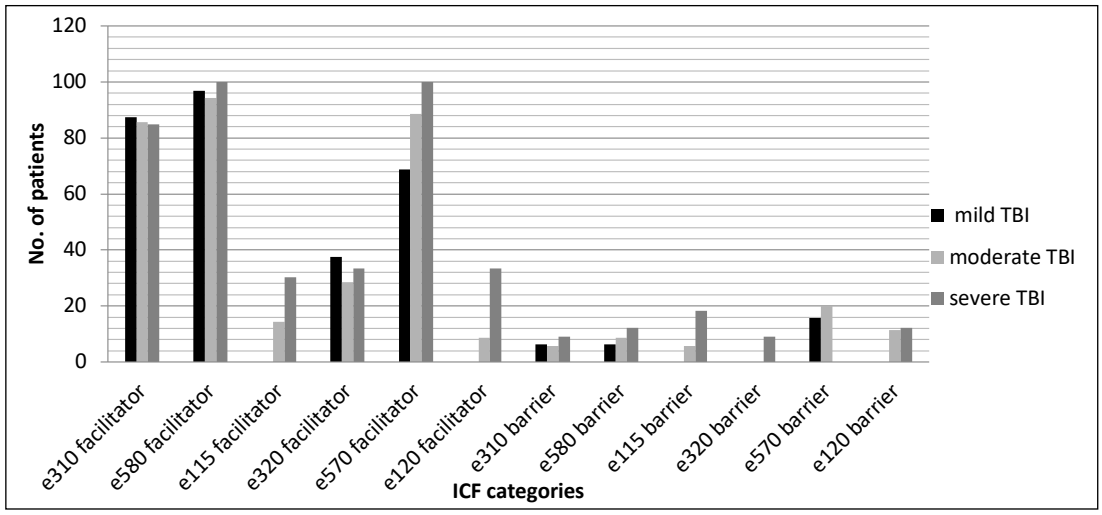

Fig 2. The proportion of patients (%) identified environmental factors (e) from the ICF Brief Core Set for TBI as relieving intermediaries or barriers.

Two categories marked as completely impaired (qualifier 4): sensation of pain (3,13% and 6,06% in the groups with mild and severe TBI, respectively), and attention functions (6,06% in the group with severe TBI).

The most common lesions of attention, memory, information processing speed, and executive functions in patients with consequences of TBI, registered in many studies. They are considered to be a consequence of damage to temporal lobe, frontal lobe and white substance of the brain [7]. The identification of these changes was expected, and the fact that the ICF Brief Core Set for TBI contains the detailed description of this area of disturbances, supports the utility of this tool for correct identification of the most common problems in patients with craniocerebral trauma.

In «Activity and Participation» section, in addition to the mentioned above, a significant amount of disturbances were recorded in categories d845 «acquiring, keeping and terminating a job» and d920 «recreation and leisure». In the group of patients with severe TBI in the past history for 15,15% of subjects with category d845 and for 12,12% of subjects with category d920 these functions were identified as completely impaired (qualifier 4). This fact indicates the extreme importance of this group of disorders for developing rehabilitation programs for patients with consequences of TBI.

Impaired categories of activity and participation mostly reflect the complex activities that ensure the inclusion of the subject into various social processes: interpersonal interactions, family and working relationships, rest and leisure. Existing emotional disorders and cognitive dysfunctions might be probable reasons for the changes mentioned before. Such disturbance of integration in society is common for all patients after head injury [8]. Household activity is restored generally to its original level. Meanwhile, public and professional activities remain low, which correlates with the data in foreign publications [9] and was demonstrated in the current study. More than one thirds of all patients paid attention to disturbances even in the recreation and leisure category. According to other authors the percentage of passive activities, such as watching television, is increasing in this category of patients in proportion to the decrease in more active and diverse

leisure activities [10]. Physical barriers (accessibility) and lack of communication skills in patients may be additional factors in the reduction of social activity.

The increase in the amount and severity of disturbances with increasing severity of craniocerebral trauma had been established in all categories, except d720 «complex interpersonal interactions» and d760 «family relationships». Patients with severe brain contusion in the past history identified problems in sections d720 and d760 even less often than patients with mild and moderate TBI. The exception may be stipulated by more advanced disorders of the cognitive functions, reduction of criticism to his/her condition and low level of claims the individuals.

Figure 2 presents the following ICF categories of patients with TBI: e310 next of kin, e580 medical services, systems and policies, products and technologies e115 for personal use in everyday life, e320 friends, e570 social welfare services, systems and policies, products and technologies e120 for personal internal and external mobility and transport. The influence of environmental factors on the functioning of patients with a history of TBI was also assessed in our study (Fig. 2), since they can clearly affect the outcome of rehabilitation [11].

Patients of all groups identified the family and close relatives, healthcare service and social welfare services as the most frequent relieving factors of life activity. The large percentage of indications on the relieving function of social services in the groups under study is connected with the significant proportion of patients being recognized as disabled. They had been receiving financial support for the certain period of time. It is also quite important fact, that patients mostly identified environmental factors as mediators, but not as barriers. Definition of environmental factors as barriers in each category did not exceed 20%.

DISCUSSION

Traumatic brain injury is a major cause of disability in both children and young adults. TBI is an important global public health problem and represents a major contributor to mortality and disability among all trauma-related injuries [12]. It is estimated that sixty-nine million patients suffer from head injuries worldwide each year [13].

As the number of people suffering from TBI has increased significantly in recent years, the multiple impairments in these patients make designing a rehabilitation process a challenge for practitioners [14].

In this regard, the issues of treatment and rehabilitation are particularly important for these patients. The success of treatment and rehabilitation measures is possible with a successful classification of the existing impairments that need to be addressed by these measures.

The International Classification of Functioning, Disability and Health (ICF) is a framework for describing the health-related functioning of patients, including those with TBI. It provides a common language and framework for describing a person's level of functioning in their unique circumstances or, in other words, what a person with a particular health condition can do under standardized conditions (their level of capability) [15]. In this regard, this classification is actively used by researchers in neurology [16-20].

Our study determined from the ICF perspective that memory function, emotional function, pain perception, attention function, brain structure, complex interpersonal interactions, and family relationships were the most frequent categories in trauma patients with alterations. Similar results were also obtained in other studies [2].

Thus, the use of ICF Brief Core Set for TBI provides a fairly accurate description of the functioning and health of patients in remote period of craniocerebral trauma with an integrative model. It assumes that individual performance is the result of interactions between health condition and environmental factors. Regarding the results of the study it should be noted that they reflect the state of the problem in Ukraine, so cultural and national characteristics could influence the results.

CONCLUSIONS

1. The most common problems in the functioning and health status of patients in remote period of TBI, along with the influencing factors have been identified in the study. The most frequent categories with alterations were memory functions, emotional functions, sensation of pain, functions of attention, brain structure, complex interpersonal interactions, and family relationships. This result indicates that not all the rehabilitation needs of patients recovering from TBI are met. The most frequent relieving factors of life activity were the family and close relatives, healthcare service and social welfare services.
2. The use of the ICF Brief Core Set for assessing the subjects with TBI in past history provides a convenient procedure to standardize and structure functioning description. Information collected by the ICF Brief Core Set may be used for different purposes: clinical assessment, administration of medical services, planning and implementation of rehabilitation and evaluation of results, in scientific research, reports and health care statistics.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

The association of TLR4 gene polymorphisms with the severity of peritonitis in acute inflammatory diseases of the abdominal cavity organs

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ABSTRACT

Aim: To determine the role of TLR4 gene polymorphisms as risk factors for peritonitis severity in patients undergoing surgery for acute inflammatory diseases of the abdominal cavity.

Materials and Methods: The study included 139 patients who were operated on for acute abdominal diseases (acute appendicitis and cholecystitis, perforated gastric or duodenal ulcer, etc.). Depending on the number of points on the modified APACHE II scale, patients were divided into two groups: Group 1 - 1-3 points (63 patients, 45.3%) and Group 2 - 4 or more points (76 patients, 54.7%). Polymorphisms rs1927911, rs2149356 and rs4986790 were determined by polymerase chain reaction.

Results: The rs1927911 polymorphism of the TLR4 gene was protective for the development of peritonitis (according to the allelic model, OR 0.48; 95% CI 0.27-0.84; p=0.015). Regression analysis revealed a reduced (p=0.015) risk of severe peritonitis in rs1927911 A/A or G/A genotype carriers (OR 0.42; 95% CI 0.21-0.84) compared with G/G genotype carriers. There was no effect on the severity of peritonitis of TLR4 polymorphisms rs2149356 and rs4986790. There was a tendency to increase the frequency of the mutant G rs4986790 allele in patients with severe peritonitis ($\chi 2=2.17$; $p<0.001$). The analysis of the association of TLR4 gene polymorphisms with the phenotype of patients showed that carriers of mutant homozygotes and heterozygotes in the presence of severe peritonitis were older, had a tendency to coagulopathy, higher leukocytosis and leukocyte clotting rate.

Conclusions: Thus, the importance of TLR in the development of severe peritonitis was confirmed and the protective role of the rs1927911 promoter polymorphism was established.

KEY WORDS: regression analysis, peritonitis, rs4986790, rs1927911, rs2149356

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INTRODUCTION

The high mortality rate in peritonitis, which ranges from 19% to 80%, makes it one of the most serious complications of abdominal diseases [1, 2].

Toll-like receptors (TLRs) are a family of so-called "pattern recognition receptors" that trigger cellular inflammatory and immune responses in response to exogenous and endogenous proinflammatory factors [3]. Activation of the proinflammatory signaling pathway mediated by Toll-like receptor 4 (TLR4) plays an important role in acute inflammation, sepsis, and chronic inflammatory diseases. Highly specific antibodies to TLR4 inhibited lipopolysaccharide-induced production of tumor necrosis factor-α, interferon-β, and interleukin-6 in mouse peritoneal macrophages by reducing phosphorylation of NF-κB and mitogen-activated protein kinase [4].

Changes in TLR function caused by genetic polymorphism can determine the incidence or severity of acute inflammatory diseases, as shown by acute pancreatitis [5] and inflammatory bowel disease in children [6].

Polymorphism of genes involved in the body's defense may be associated with the severity of local infection-inflammation in humans, in particular in acute appendicitis, which was shown for the IL-6 gene (-174G>C), but not for the TLR4 gene (896 A>G) [7].

On the other hand, a systematic review and meta-analysis that included the results of 1476 patients with urinary tract infection and 1449 healthy control patients showed that in Asian populations, the rs4986790 polymorphism of the TLR4 gene was associated with the risk of urinary tract infection [8].

A recent meta-analysis showed the role of TLR gene polymorphisms in inflammatory bowel disease in Caucasians [9]. Significant associations were found for the TLR1 rs5743611, TLR4 rs4986790, TLR4 rs4986791, and TLR6 rs5743810 polymorphisms. In addition, the TLR4 rs4986790 polymorphism was significantly associated

with the risk of inflammatory bowel disease in West Asians. The influence of TLR4 gene polymorphism on the risk of gastric cancer in northeastern China has also been shown [10]. Carriers of the mutant homozygote rs1927911 had a significantly reduced risk of the disease (OR 0.37; 95% CI 0.21-0.67; P=0.001).

AIM

The aim of the study was to determine the role of TLR4 gene polymorphisms as risk factors for peritonitis severity in patients undergoing surgery for acute inflammatory diseases of the abdominal cavity.

MATERIALS AND METHODS

A single-center, randomized, single-instance, open-label observational study was conducted on the basis of the Brovary Multidisciplinary Clinical Hospital in the period from 09.09.2021 to 24.10.2022. Patients were examined in accordance with the Declaration of Helsinki of the World Medical Association (Seoul, 2008), orders of the Ministry of Health of Ukraine (№ 281 of November 01, 2000, № 355 of September 25, 2002, № 356 of May 22, 2009 as amended by the order of the Ministry of Health of Ukraine № 574 of August 05, 2009, № 1118 of December 21, 2012).

All patients underwent clinical, laboratory, and genetic testing. All patients gave informed consent to participate in the study. The material for this article was based on the medical records of inpatients and the results of laboratory and genetic tests.

Inclusion criteria: patients with peritonitis over 18 years of age.

Criteria for non-inclusion in the study: patients with peritonitis of gynecological genesis, acute pancreatitis.

The study involved 139 patients who were operated on for acute abdominal diseases, including 71 patients with acute appendicitis, 51 with acute cholecystitis, 10 with perforated gastric or duodenal ulcer, 4 with tumor perforation, 1 with small intestine perforation, 1 with hernia, and 1 with cryptogenic peritonitis. Depending on the number of points on our modified APACHE II scale (Acute Physiology and Chronic Health Evaluation) [11], patients were divided into two groups: Group 1 - 1-3 points (63 patients, 45.3%) and Group 2 - 4 or more points (76 patients, 54.7%).

During the operation, the prevalence of the inflammatory process in the peritoneum (local, diffuse, spilled or general), the nature of the exudate (serous, serous-fibrinous, fibrinous-purulent, purulent, fecal or hemorrhagic), the stage of peritonitis (reactive, toxic or terminal) were determined. Prothrombin index (PTI, %), international normalized ratio (INR, units), prothrombin time (PT, min), fibrinogen content (g/l), as well as leukocyte count (G/l) and erythrocyte sedimentation rate (ESR, mm/h) were determined in the blood by biochemical laboratory methods.

TLR4 gene polymorphisms rs1927911 (Intron; Chr:9.117707776), rs2149356 (Intron; Chr:9. 117711921) and rs4986790 (896A/G; chr9:117713024; Asp299Gly) were determined by real-time polymerase chain reaction using Gene Amp® PCR System 7500 amplifier (Applied Biosystems, USA) and TaqMan Mutation Detection Assays Life-Technology (USA). Genomic DNA was extracted from venous blood using the PureLink® Genomic DNA Kit For Purification of Genomic DNA (INVITROGEN, USA).

Statistical processing of the results of the study was performed using EZR v.1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) [12]. The Shapiro-Wilk test was used to check the distribution of quantitative indicators for normality; the distribution law differed from the normal one, so the median (Me) and the first and third quartiles (Q1-Q3) were calculated for presentation, and the Mann-Whitney, Wilcoxon, and Kruskal-Wallis ranked analysis of variance were used to compare samples. Differences in genotype and allele frequencies were compared by Fisher's exact method and Pearson's $\chi 2$ test. The statistical significance of differences in the distribution of genotype and allele frequencies in the case-control group was evaluated in the contingency tables (3×2 and 2×2, respectively). The degree of association of genotypes and alleles with the severity of peritonitis was determined by calculating the odds ratio (OR) and 95% confidence interval (95% CI). For regression analysis, the method of constructing logistic regression models was used [13], the initial sign was Y=0 (APACHE II 1-3 points - 63 patients), Y=1 (APACHE II 4 and more points - 76 patients). In all cases of statistical evaluation, the value of $p<0.05$ was considered significant.

RESULTS

When comparing the distribution of genotypes in patient groups, it was found (Table 1) that in patients of group 2, a decrease in the frequency of the G/A heterozygote, minor homozygote A/A and allele A was noted compared with patients of group 1, which was statistically significant at p=0.040 (for genotypes) and p=0.015 (for alleles).

Comparison of the dominant and recessive inheritance model showed statistical significance (p=0.022) of the dominant model (Table 2).

Table 1. Influence of the distribution of frequencies of genotypes and alleles of rs1927911 of the TLR4 gene on the severity of peritonitis and the degree of their association with the disease

Genotypes Alleles	Group, n (f)		χ^2	p	OR	95% CI
	2-nd	1-st				
G/G	53 (0,70)	31 (0,49)	6,42	0,040	Reference	
G/A	20 (0,26)	26 (0,41)			0,45	0,22 – 0,94
A/A	3 (0,04)	6 (0,10)			–	–
G	126 (0,83)	88 (0,70)	5,91	0,015	Reference	
A	26 (0,17)	38 (0,30)			0,48	0,27 – 0,84

Notes: n - number; f - frequency; χ2 - Pearson's correction for continuity; p - statistical significance of differences between groups; OR - odds ratio; 95% CI - 95% confidence interval for OR.

Table 2. Influence of the frequency distribution of TLR4 gene rs1927911 genotypes on the development of peritonitis (dominant and recessive models of inheritance)

	Genotypes 2-a	Group, n (f)		χ^2	p	OR	CI% BI
		1-a					
Dom.	G/G	53 (0,70)	31 (0,49)	5,24	0,022	Reference	
	G/A+A/A	23 (0,30)	32 (0,51)			0,42	0,21–0,84
Rec.	G/G+G/A	73 (0,96)	57 (0,90)	0,97	0,326	Reference	
	A/A	3 (0,04)	6 (0,10)			–	–

Notes: n - number; f - frequency; χ2 - Pearson's correction for continuity; p - statistical significance of differences between groups; OR - odds ratio; 95% CI - 95% confidence interval for OR.

Table 3. Influence of genotypes of rs1927911 polymorphism of TLR4 gene on the studied indicators

Indicator	Group	Genotypes		p
		G/G	G/A+A/A	
Age, years	1-st	44,2±16,7	41,4±14,8	0,489
	2-nd	47,5±17,1	51,8±13,7	0,282
p*		0,398	**0,011**	
PTI, %	1-st	105,0 (92,4–120,0)	98,6 (88,1–111,1)	0,202
	2-nd	87,9 (75,6–96)	88,4 (77,6–101,9)	0,931
p*		0,006	0,211	
INR	1-st	0,989 (0,940–1,05)	1,034 (0,970–1,080)	0,306
	2-nd	1,106 (1,055–1,163)	1,12 (1,020–1,160)	0,972
p*		**0,006**	0,134	
PT, min.	1-st	11,5 (10,3–11,9)	10,6 (10,3–11,0)	0,737
	2-nd	12,2 (11,5–13,0)	12,5 (10,7–13,3)	>0,999
p*		0,066	**0,020**	
Fibrinogen, g/l	1-st	8,41 (3,87–10,59)	4,58 (4,30–4,86)	0,845
	2-nd	5,13 (4,30–6,60)	4,22 (3,87–4,77)	0,702
p*		0,926	0,688	
Leukocytes, g/l	1-st	9,6 (6,4–12,6)	10,8 (6,8–12,6)	0,417
	2-nd	14,2 (11,5–17,5)	13,9 (11,1–17,5)	0,826
p*		<0,001	0,005	
ESR, mm/h.	1-st	13,9 (4,0–16,5)	21,3 (7,0–35,0)	0,184
	2-nd	25,5 (14,5–36,5)	42,0 (33,3–52,0)	0,400
p*		0,161	0,086	

Notes: p - statistical significance of differences in the group; p* - statistical significance of differences between groups. In the case of a normal distribution law, M±SD is presented, Student's test is used for comparison; in the case of a distribution law other than normal, Me (QI - QIII) and the Mann-Whitney test are used.

Table 4. Influence of rs2149356 genotype frequency distribution of TLR4 gene on the severity of peritonitis

Genotypes Alleles	Group, n (f)		χ^2	p	OR	95% CI
	2-nd	1-st				
G/G	33 (0,434)	28 (0,444)	0,02	0,992	Reference	
G/T	33 (0,434)	27 (0,429)			–	–
T/T	10 (0,132)	8 (0,127)				
G	99 (0,651)	83 (0,670)	0,00	>0,999	Reference	
T	53 (0,349)	43 (0,330)			–	–

Notes: n - number; f - frequency; χ2 - Pearson's correction for continuity; p - statistical significance of differences between groups.

Table 5. Influence of the frequency distribution of TLR4 gene rs4986790 genotypes on the severity of peritonitis

Genotypes Alleles	Group, n (f)		χ^2	p	OR	95% CI
	2-a	1-a				
A/A	57 (0,750)	52 (0,825)	2,97	0,227	Reference	
A/G	16 (0,211)	11 (0,175)			–	–
G/G	3 (0,039)	0 (0,000)				
A	130 (0,855)	115 (0,913)	1,66	0,198	Reference	
G	22 (0,145)	11 (0,087)			–	–

Notes: n - number; f - frequency; χ2 - Pearson's test with correction for continuity; p - statistical significance of differences between groups; OR - odds ratio; 95% CI - 95% confidence interval for OR

Table 6. Analysis of single-factor logistic regression models for predicting the risk of severe peritonitis by polymorphic genotypes of the TLR4 gene

Factor attribute		Model coefficient, b±m	Significance level of the difference between the OR and 1, p	The model's odds ratio, OR (95% CI)
rs1927911	*G/G*	Reference		
	A/A+G/A	-0,87 ± 0,35	0,015	0,42 (0,21 – 0,84)
rs2149356	*G/G*	Reference		
	G/T	0,04 ± 0,37	0,921	–
	T/T	0,06 ± 0,54	0,913	–
rs4986790	*A/A*	Reference		
	G/G+G/A	0,45 ± 0,42	0,284	–

Thus, the presence of the mutant allele A in the TLR4 gene rs1927911 genotype (for carriers of G/A and A/A genotypes) reduced the likelihood of severe peritonitis (OR 0.42; 95% CI 0.21-0.84), which allowed us to consider this polymorphism a prognostic factor.

The analysis of the association of rs1927911 with the phenotype is shown in Table 3. When stratifying patients by groups and genotypes of rs1927911, it was found that the oldest patients were carriers of the mutant allele A.

The PTI and INR were different in carriers of the ancestral G/G genotype, with a lower PTI (p=0.006) and higher INR (p=0.006) in patients with severe peritonitis than in those without. The PI was higher in patients carrying the A allele in the presence of severe peritonitis (p=0.020). The detected shifts indicated the presence of coagulopathy with a predisposition to hemorrhagic syndrome. Leukocytosis in the presence of severe peritonitis was higher in carriers of all genotypes (p≤0.005).

In the present study, there was no significant difference in the distribution of TLR4 rs2149356 and rs4986790 genotypes and their influence on the development of peritonitis (Table 4 and Table 5).

The analysis of the association of rs2149356 and rs4986790 with the phenotype of patients showed that mutant homozygotes and heterozygotes in the presence of severe peritonitis were older, had a lower PTI and higher INR, WBC, leukocytosis and ESR (p<0.05), which was similar to the distribution for rs1927911. Interestingly, in patients carrying the mutant homozygote G/G and heterozygote A/G rs4986790, who had mild peritonitis, ESR was the lowest among all groups stratified by diagnosis and genotype (Me 5.83 mm/h; QI-QIII 2 mm/h - 8 mm/h).

To confirm the role of the identified polymorphisms of the TLR4 gene, we used the method of building logistic regression models [13]. The analysis was performed to

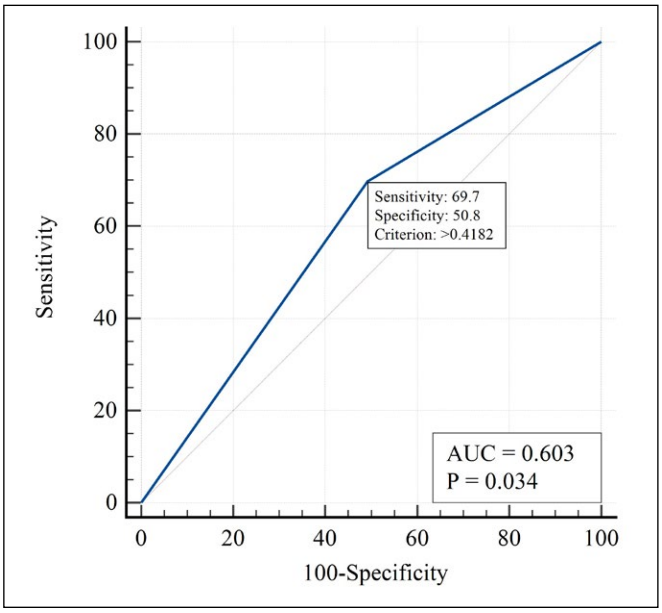

Fig. 1. ROC curve for predicting the risk of severe peritonitis by TLR4 rs1927911 genotypes.

identify the association of the risk of severe peritonitis with the factor characteristics for all patients. Table 6 shows the results of univariate analysis of the association of peritonitis risk with polymorphic genotypes of the TLR4 gene.

The analysis revealed a reduction (p=0.015) in the risk of severe peritonitis in carriers of the rs1927911 A/A or G/A genotypes (OR 0.42; 95% CI 0.21-0.84) compared with carriers of the rs1927911 G/G genotype.

Figure 1 shows the operating characteristics curve for this test.

The area under the ROC curve AUC=0.60 (95% CI 0.52-0.69), which indicated the presence of an association of severe peritonitis risk with rs1927911. When choosing the optimal threshold (rs1927911 G/G genotype), the test sensitivity was 69.7% (95% CI 58.1%-79.8%), specificity 50.8% (95% CI 37.9%-63.6%).

DISCUSSION

It is believed that the TLR4 rs4986790 gene polymorphism is a functional polymorphism that leads to a decrease in receptor sensitivity [10, 14]. In our studies, the frequency of the G rs4986790 mutant allele in patients of group 2 increased significantly ($\chi 2=2.17$; $p<0.001$), but the association with the disease for rs4986790 in this sample of patients was not confirmed (p=0.198; see Table 5). Thus, within the framework of the results obtained, it was possible to assert only the existence of a tendency for this polymorphism to be associated with severe peritonitis. This assumption is confirmed by the absence of an increase in ESR in patients carrying the mutant homozygote G/G and heterozygote A/G rs4986790 who had mild peritonitis.

A recent meta-analysis of 38 studies (10970 cases and 7061 controls) provided evidence that TLR4 rs4986790 is associated with susceptibility to Crohn's disease and ulcerative colitis in Caucasians but not in Asians [15].

The suppression of the immune response in the absence of the TLR4 gene was shown in another study [16]. In experiments with TLR4-deficient (TLR4-/-) mice, it was found that chronic inflammation and infiltration of the colon by macrophages, intestinal fibrosis and collagen deposition were reduced in a model of chronic colitis and colon fibrosis using 3% sodium dextran sulfate. In addition, the production of tumor necrosis factor-α, interleukin-12p40, and transforming growth factor-β was reduced in TLR4-deficient peritoneal macrophages.

Blockade of TLR4 by antibodies differentially suppressed the bacteria-induced production of profibrotic and inflammatory mediators by peritoneal leukocytes in peritoneal dialysis patients with uremia [17]. In addition, antibodies against TLR4 decreased the profibrotic responses of uremic leukocytes to endogenous components, whereas increased TLR-mediated inflammation increased fibrosis in vivo.

Analysis of the gene expression profile using the Gene Expression Omnibus database identified a panel of 446 key genes and relevant pathways involved in the formation of inflammation in postoperative peritoneal adhesion [18]. Functional analysis suggested that these genes were enriched in the TLR signaling pathway via myeloid differentiation primary response protein 88 (MyD88) and nuclear factor kappa B (NF-κB) - the TLR4/MyD88/NF-κB proinflammatory pathway/inflammatory cytokines/peritoneal adhesion. It was also found that the TLR4/MyD88/NF-κB signaling pathway was activated in the acute phase of appendicitis [19].

These results explain the general importance of TLR gene polymorphisms that cause a decrease in its functional activity. For example, TLR4 knockout enhances the clearance of infectious bacterial species that show excessive amounts in the abdominal cavity of mice after ligation and puncture of the cecum [20].

In our studies, we found an association of severe peritonitis with the promoter polymorphism rs1927911 of the TLR4 gene in a dominant model (OR 0.42; 95% CI 0.214-0.84; p=0.022). This polymorphism was protective for the development of severe peritonitis, which also confirmed the negative significance of wild-type TLR4 for the development of acute inflammation. The TLR4 gene polymorphism affects intracellular signal transduction and, as a result, changes the patterns of immune response not only in inflammatory but also in cancer, in particular cervical cancer [21].

Thus, our data confirmed the generally accepted view of the key role of TLR in the development of acute peritonitis and established the protective role of the promoter polymorphism rs1927911 and the tendency to risk value of the polymorphism rs4986790.

CONCLUSIONS

1. The rs1927911 polymorphism of the TLR4 gene was protective for the development of severe peritonitis (according to the allelic model, OR 0.48; 95% CI 0.27-0.84; p=0.015). Regression analysis revealed a decrease (p=0.015) in the risk of severe peritonitis in carriers of rs1927911 A/A or G/A genotypes (OR 0.42; 95% CI 0.21-0.84) compared with carriers of the G/G genotype.
2. There was no effect of rs2149356 and rs4986790 polymorphisms of the TLR4 gene on the development of peritonitis. There was a tendency to increase the frequency of the mutant G rs4986790 allele in patients with severe peritonitis ($\chi 2=2.17$; $p<0.001$).
3. The analysis of the association of TLR4 gene polymorphisms with the phenotype of patients showed that carriers of mutant homozygotes and heterozygotes in the presence of severe peritonitis were older, had a lower PTI and higher INR, PF, leukocytosis and ESR.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Comparative analysis of the quality of life of women who left the territory of Ukraine during the ongoing Russia – Ukraine war and women who stayed at their homes

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DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: To investigate the quality of life of women who left Ukraine and those who did not leave their homes under the threat of war.

Materials and Methods: We used the WHOQOL-100 questionnaire for quality assessment. 376 young women (aged 25-44) were interviewed using a Google questionnaire (WHOQOL BREF). The respondents were divided into 2 groups: group 1 – women who left the territory of Ukraine during the war (n-176); group 2 - women who did not leave their homes (n-200).

Results: The general level of quality of life for group 1 (62.9% ± 9.3) was slightly lower than group 2 (66.7% ± 9.1). In terms of quality of life, group 2 prevails over group 1 in the domain of microsocial support.

Conclusions: Therefore, women who did not leave their homes during the full-scale invasion of Russia on the territory of Ukraine rate their quality of life higher than women who left the territory of Ukraine. Respondents of group 2 are more satisfied with their social support, sexual life, support from friends, enjoy life more than respondents of group 1.

KEY WORDS: quality of life, women, war in Ukraine

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INTRODUCTION

About 13.7 million Ukrainians left their homes, more than 5.6 million of them left Ukraine, 90% of the displaced people are women and children as of May 2022, according to the International Organization for Migration (IOM) [1]. World Health Organization (WHO) data, as of November 30, 2022, shows that more than 15 million Ukrainians were forced to leave their homes. Of course, war and displacement, whether within a country or abroad, affect the quality of life.

The concept of "quality of life" (QoL) has become an integral part of the healthcare system and clinical, medical and social research in the last decade [1-5]. The gradual replacement of the biomedical model of health by the biopsychosocial model caused the need to take into account a person's subjective perception of their well-being. In 1982, Kaplan and Bush introduced the term "health-related quality of life" (the quality of life is related to health), which made it possible to distinguish the parameters that describe the state of health, care for it and the quality of medical care from the general concept of life quality.

The basis for the formation of the term *quality of life* in medicine is the definition of health given by the WHO back in 1948: "health is a state of complete physical, mental and social well-being, and not just the absence of disease and or infirmity" [2]. The main criteria of QoF were developed by WHO: physical, psychological, level of independence, social life, environment and spirituality.

The most rational and actual method of the quality of life analysis is the use of standardized questionnaires in research, which are necessary to obtain results that can be compared with each other, regardless of the country of study [6, 7]. There is a fairly significant number of HRQOL assessment questionnaires (more than 4,000), which can be divided into the following groups: universal (general) for children and adults and special (by fields of medicine, different diseases, treatment methods, individual patient's condition). According to the structure, questionnaires are divided into profile (include several scales that describe different QoL parameters, or evaluate each QoL component separately) and indices (contains a single numerical value). To assess the state of quality of life, the data obtained in the questionnaire are accordingly converted into separate numerical values (points), which allow for their statistical processing. General questionnaires are used to assess the quality of life of both healthy and unhealthy people. They

can be used in population studies to develop standards and establish various changes in the quality of life in various patients (individually or in groups), as well as to evaluate the effectiveness of various health care programs in general [2, 3].

The advantage of general questionnaires is that they allow a comparative assessment of the different medical programs impact on the effectiveness of HRQOL in individual patients and in the population as a whole [2, 3].

The process of cultural adaptation of questionnaires is extremely complex and requires the close cooperation of international developers, translators, and psychologists in order to use them in different ethnic and cultural and social groups of the population [2,7-10].

Today, a significant number of questionnaires in full and shortened versions are widely used in Ukraine, which have undergone cultural adaptation [2,4,8]. This allows them to be used in medical practice in our country. The most commonly used general quality of life questionnaires are: World Health Organization's Quality of Life - WHOQOL-100 (developed by WHO specialists), SF-36 (Item Short Health Status Survey), «EuroQoL (EQ-5D)», Q-LES-Q and others, in full and shortened versions [2,3,9,11, 12].

The WHO quality of life questionnaire - WHOQOL-100 was being created for 5 years simultaneously in the main world languages in 15 WHO centers in all parts of the world, in countries with different economic levels and cultural traditions (WHOQOL - World Health Organization's Quality of Life) according to a single methodology. From more than 1,500 questions proposed at the beginning of the questionnaire, the best 100 were selected, primarily based on the respondents' reports.

The sample was about 4,500 people. Also, at the same time, a shortened version of the WHOQOL-BREF was created, consisting of only 26 questions and 4 domains (physical and psychological well-being, self-perception, microsocial support, social well-being). It is a reliable and independent tool for assessing the quality of life of people regardless of the social, cultural, demographic and political context [6,7,13-15].

AIM

The aim of our study: to investigate the quality of life of young women who were forced to leave the country after February 24, 2022, and those who did not leave their home in Ukraine.

MATERIALS AND METHODS

376 young women were interviewed using WHOQOL-BREF. The survey is anonymous and voluntary. The questionnaire was distributed in the form of a Google form. The criteria for inclusion in the study were 25-44 years old women with higher education who understand the content of the questionnaire. Exclusion criteria for all participants were as follows: candidates who had difficulty understanding the content of the questionnaire, found it impossible to complete the questionnaire, or candidates who have a disease that negatively affects the quality of life (absence of acute or exacerbation of chronic physical or mental diseasess at the time of the survey). The respondents were divided into 2 groups: group 1 (n=176) – women who left the territory of Ukraine during the war (temporarily living in the territory of the European Union); group 2 (n=200) - women who did not leave their homes. We chose the WHOQOL-BREF questionnaire, having obtained official permission for its use. All responses are evaluated on a 5-point scale: the higher the score – the better the quality of life. The points are calculated on a scale from 0 to 100. The survey was answered by the respondents assessing their feelings during the preceeding four weeks. The collection of respondents lasted from 02/12/2022 to 30/12/2022.

Statistical processing of the research results was carried out using the Statistica 10 software package. As a measure of internal consistency of the scale, Cronbach α was calculated for the general totality, each domain and facet. For the entire sample, Cronbach α values were acceptable (> 0.7). Quantitative features are presented as arithmetic mean ± standard error. Statistical probability was calculated using Student's t-test. Odds ratios with 95% confidence interval for percentage relative values of the results. The difference in values was considered probable at $p \leq 0.05$.

RESULTS

Among the interviewed women, 81.9% (308 women) had one higher education and 18.1% (68) had two or more higher educations. 78.5% (295) women had an average level of professional activity, 9.3% (35) - high, and 12.25 (46) - low. Finally, 58.5% women (220) assessed their income level as average, 39.45 % (148) as low, and 2.1% people (8) as high.

The results of our study showed the general level of quality of life for group 1 is 62.9% ± 9.3; group 2 – 66.7% ±9.1 ($p = 0.42$, $t = 0.79$, Cronbach $\alpha > 0.7$). As we can see, according to the assessment of the general level of QoL, group 2 slightly outperforms group 1, however, this difference is not statistically significant.

If we compare the QoL between the groups by domains and in absolute numbers, we can see that women in group 2 rate their QoL slightly higher than women from group 1, it is statistically significant in all

Table 1. Comparison of quality of life of women who left their country and those who stayed at their homes during the war in Ukraine, according to the domains

Domain	Group 1, abs.	Group 2, abs.	p	t	Group 1, %, confidence interval	Group 2, %, confidence interval
Physical and psychological well-being	19,6±2,9	20,5±3,5	*0,04	2,1	56,1±8,3 (54,9; 57,4)	58,7±10 (60,5; 55,5)
Self-perception	19,5±3	20,4±3,0	*0,02	2,3	65,1±9,9 (63,6; 66,6)	69,0±10,1 (66,9; 71,1)
Microsocial support	9,5±2,6	10,8±2,6	*0,0003	3,7	62,5±17,3 (66,1;60,9)	72,0±17,3 (68,4;75,6)
Social well-being	26,8±5,4	27,9±4,5	*0,05	1,9	67,1±13,5 (65,1; 69,1)	70,1±11,2 (67,6; 72,4)

* $p \leq 0,05$.

Table 2. Comparison of quality of life of women who left their country and those who stayed at their homes during the war in Ukraine, according to the facets

№	Question	Group 1	Group 2	p	t
1	How would you rate your quality of life?	3,5	3,5	0,9	0,1
2	How satisfied are you with your health?	2,9	3,2	*0,02	2,3
3	To what extent do you feel that physical pain prevents you from doing what you need to do?	3,9	3,8	0,2	1,3
4	How much do you need any medical treatment to function in your daily life?	3,8	4,0	0,08	1,7
5	How much do you enjoy life?	3,0	3,6	*0,0005	6,2
6	To what extent do you feel your life to be meaningful?	3,7	3,7	0,3	1,0
7	How well are you able to concentrate?	3,1	3,5	*0,001	3,3
8	How safe do you feel in your daily life?	3,4	2,9	*0,000	4,7
9	How healthy is your physical environment?	3,6	3,5	0,3	1,0
10	Do you have enough energy for everyday life?	2,8	3,2	*0,02	3.1
11	Are you able to accept your bodily appearance?	3.4	3,7	0,1	1,6
12	Have you enough money to meet your needs?	3,3	3,2	0,7	0,4
13	How available to you is the information you need in your daily life?	3,8	4,1	*0,005	2,9
14	To what extent do you have the opportunity for leisure activities?	2,7	2,9	0,3	1,0
15	How well are you able to get around physically?	3,6	3,7	0,6	1.2
16	How satisfied are you with your sleep?	2,9	2,9	0,3	1,1
17	How satisfied are you with your ability to perform your daily living activities?	3,3	3,4	0,5	0,7
18	How satisfied are you with your work capacity?	2,8	3,3	*0,0005	3,5
19	How satisfied are you with yourself?	3,1	3,4	*0,03	2,2
20	How satisfied are you with your personal relationships?	3,2	3,6	*0,009	2,2
21	How satisfied are you with your sexual life?	3,0	3,4	*0,03	2,2
22	How satisfied are you with the support you get from your friends?	3,4	3,9	*0,000	4,2
23	How satisfied are you with the conditions of your living place?	3,4	3,8	*0,0001	3,9
24	How satisfied are you with your access to health services?	3,0	3,8	*0,000	5,7
25	How satisfied are you with your transport?	3,7	3,8	0,4	0,8
26	How often do you have negative emotions such as blue mood, despair, anxiety or depression?	2,7	3,2	*0,000	5,1

* $p \leq 0,05$.

four domains (Table 1). In terms of QoL, group 2 prevails over group 1 in the domain of microsocial support (group 1 – 9.5, group 2 – 10.28; p = 0,02).

For a better understanding of what exactly had an impact on the quality of life of women, we compared the groups according to the survey questions and found that women from group 2 rate their satisfaction with life statistically significantly better (group 1 – 3.0; group 2 – 3.6; p=0.0005), are able to concentrate better (group 1 – 3.1; group 2 – 3.5; p=0.00q1), are more full of energy (group 1 – 2.8; group 2 – 3.2; p=0.02) and are more satisfied with their work capacity (group 1 – 2.8; group 2 – 3.3; p=0.0005). As mentioned above, respondents from group 2 significantly evaluate their quality of life higher according to the domain of microsocial support (Q 20, Q 21, Q 22) (Table 2)

It should be noted that women of group 1 feel significantly safer than women of group 2 (group 1 – 3.4; group 2 – 2.9; p=0.000), and experience anxiety and negative emotions significantly less frequently (group 1 – 2.7; group 2 – 3.2; p=0.000).

DISCUSSION

Previous studies and the bitter experience of other countries affected by armed conflicts show that at least one in five people has negative mental health consequences, and one in ten experiences these consequences has moderate or severe illness. The consequences of the impact of the war on the Ukrainian health care system were studied, in particular on the provision of medicines to patients in need of long-term therapy. [16] In connection with the war, the main negative factors in the deterioration of the quality of life of Ukrainians became lack of safety, decrease in income; problems with the supply of electricity, water and heat; general deterioration of housing conditions and the growth of overpopulation in the western regions, limiting accessibility quality medical services and other social services, etc. [17]

An analysis of the current state of regulatory and legal regulation of pharmaceutical provision of the population of Ukraine in the conditions of martial law was carried out. [17; 18] The frequency and manifestations of emotional disorders in children of Ukraine who were exposed to war factors in the occupied territory were studied. [19] There is a research of the impact of war conditions on the mental state and quality of life of women in the Persian Gulf ant it shows poorer quality of life and fatigue. However, in current research female military veterans of the 1990-1991 Persian Gulf War were involved but it is not too close in terms of representativeness. [20] The quality of life of Ukrainian women during the ongoing war was not studied, so our work is relevant. The above research samples are not fully representative for all population of Ukraine. The distribution of socio-demographic characteristics among the respondents does not reflect the distribution of these characteristics among the entire population of Ukraine.

Our research, despite expectations, not only showed us that women who left Ukraine after the start of a full-scale war have a lower quality of life, but also it helped us to understand the factors that make women who stayed in the country feel better. There is a need to continue this research due to the fact that the war continues, and the quality of life and health of a person is a very dynamic indicator.

CONCLUSIONS

According to the results of our research, despite expectations, women who did not leave their homes during the full-scale invasion of Russia on the territory of Ukraine rate their quality of life higher (66.7%) than women who left the territory of Ukraine (62.9%). The better quality of life of women who did not leave Ukraine is due to higher parameters of microsocial support components as social support, sexual life, support from friends, enjoy life.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Prodromal period of psychosis: diagnostic criteria

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ABSTRACT

Aim: To study the psychopathological mechanisms of the development of the prodromal stage of psychosis in order to identify risk factors for the formation of psychosis.

Materials and Methods: In this research 137 patients with newly diagnosed psychosis were examined: 65 patients with a diagnosis of paranoid schizophrenia; 72 patients - with a diagnosis of acute polymorphic psychotic disorder.

Results: According to the analysis of symptoms using the PANSS, the absence of signs of an anxious state, conceptual disorganization of thinking, emotional withdrowal are reliable signs of PPP in PS, and unusual thought content, absence of signs of stereotyped thinking, tension, anxiety, and hallucinations are reliable signs of PPP in APPD. According to the analysis of symptoms using the SOPS, unusual thought content/delusional ideas, bizarre thinking, social anhedonia, suspiciousness/persecutory ideas, decrease in expressiveness of emotions are reliable signs of PPP in PS, and bizarre thinking, impaired tolerance to normal stress, sleep disturbance, perceptual abnormalities/hallucinations, trouble with focus and attention are reliable signs of PPP in APPD.

Conclusions: In the process of studying the clinical-psychopathological and pathopsychological aspects of the development of the PPP, a number of risk factors for the formation of psychosis were identified. We found that he most important diagnostic signs of PPP in PS patients are: stereotyped thinking, social isolation, disorganizational thinking disorders, passive-apathetic social detachment, suspiciousness. The most informative prodromal symptoms of HP in PS patients are: conceptual disorganization of thinking, bizzare thinking, social isolation, suspiciousness/persecutory ideas, reduced expression of emotions.

KEY WORDS: paranoid schizophrenia, PANSS, prodromal period of psychosis, acute polymorphic psychotic disorder, SOPS, premorbid psychosis

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INTRODUCTION

Modern trends in medicine include prevention and early detection of both acute and chronic diseases. This greatly helps in their treatment and allows us to prevent the consequences. In the structure of psychiatric diseases, psychotic disorders continue to be one of the most disabling - they are hard to endure by patients and their families, and have a significant impact on the quality of life and social functioning. The task of studying of prodromal signs of paranoid schizophrenia or acute polymorphic psychotic disorder is quite non-trivial and requires significant efforts of scientists and clinicians [1-10].

AIM

The aim of this research was to **:** study of clinical-psychopathological and pathopsychological regularities of the development of the prodromal period of psychosis to identify risk factors for the formation of psychosis in patients with paranoid schizophrenia and acute polymorphic psychotic disorder.

MATERIALS AND METHODS

In the process of performing our work 137 patients with newly diagnosed psychosis were examined. Examination was performed in compliance with the principles of biomedical ethics, based on informed consent. Research was provided on the basis of the Ternopil Regional Clinical Psychoneurological Hospital in the period 2016-2018. Patients were divided into two groups depending on their diagnosis (based on ICD-10). The first group consisted of 65 patients diagnosed with paranoid schizophrenia (F20.0), among whom there were 44 men and 21 women; the second group consisted of 72 patients diagnosed with acute polymorphic psychotic disorder (F23.0, F23.1), among whom there were 24 men and 44 women. Inclusion criteria were inpatient status, presence of psychotic symptoms at the time of inclusion, diagnosis of paranoid schizophrenia or acute polymorphic psychotic disorder, young age of 18-45 years. Exclusion criteria from the study: presence of other mental disorders, abuse of psychoactive substances, presence of language disorders or pronounced cognitive disorders, severe somatic

condition. When examining patients, we analyzed their current mental state and the development of mental disorders through anamnestic analysis. The following methods were used for the research:

I. Clinical-psychopathological method.
II. Psychometric methods: PANSS productive and negative syndrom scale; suicidal risk scale (Los Angeles Suicidality Center); SOPS scale of prodromal symptoms; scale for determining the clinical and dynamic variant of the course of the prodromal period; structured interview scale for assessment of premorbid status - PAS-SI.
III. Psychodiagnostic methods: the questionnaire of K. Leonhard – Shmishek for determining accentuations of character; method of diagnosing the level of social frustration L.I. Wasserman in the modification of V.V. Boyko;
IV. Methods of statistical processing of the obtained data with determination of average values, their errors, informativeness measure.

RESULTS

A detailed analysis of positive and negative symptoms of PPP in patients with PS and APPD obtained using the PANSS scale showed that the most significant informative clinical signs of PPP in patients with PS are:

1. disorganized thinking of a severe and extreme degree
2. moderate emotional withdrawal.
3. moderate suspiciousness/persecution
4. moderate-severe stereotypic thinking
5. moderate-severe passive/apathetic social withdrawal.

The most informative clinical signs of PPP in patients with APPD are:

1. unusual thought content of moderate and moderate-severe severity
2. tension of moderate degree
3. anxiety of moderate-severe degree
4. hallucinations of moderate-severe degree
5. Poor attention of moderate-severe degree
6. moderate-severe excitement

According to the results of the analysis of the intensity and qualitative composition of prodromal symptoms of psychotic disorder of the SOPS scale of prodromal symptoms, the most informative prodromal symptoms of acute psychosis (AP) in patients with PS are:

1. moderately severe unusual thought content/delusional ideas (DC-(-4.06), KM-0.44, $p<0.002$);
2. questionable presence of bizarre thinking (DC-(-3.45), KM-0.29, $p<0.01$);
3. social anhedonia of an moderate degree of severity (DC-(-3.08), KM-0.26, $p<0.01$);
4. suspiciousness/persecutory ideas of a moderate degree of severity (DC-(-3.04), KM-0.24, $p<0.05$);
5. decrease in expressiveness of emotions (DC-(-8.49), KM-2.95, $p<0.05$).

According to the results of the statistical analysis, the most reliable prodromal symptoms of AP in patients with APPD are:

1. bizarre thinking of mild and moderate degree (DC-3.63, KM-0.33, $p<0.007$);impaired tolerance to normal stress of moderate and severe degree (DC-3.01, KM-0.32, $p<0.004$);
2. moderate sleep disturbance (DC-3.54, KM-0.27, $p<0.02$);
3. perceptual abnormalities/hallucinations of mild severity (DC-3.31, KM-0.23, $p<0.02$);
4. trouble with focus and attention of mild severity (DC-2.57, KM-0.17, $p<0.03$).

The degree of severity of groups of symptoms of patients with PS and APPD in the prodromal period is presented in Fig 1.

As evidenced by the data presented in fig 1, negative symptoms predominate in PPP patients - 3.3 ± 1.2 points ($p<0.05$), while in patients with APPD in the prodrome of psychosis, symptoms of disorganization (2.9 ± 0.7 points , at $p<0.05$) and general symptoms (2.7 ± 1.3 points, at $p<0.05$) are most pronounced.

Within the framework of the clinical-psychopathological method, we studied the structure of the dynamics of the flow of PPP. The study showed that the continuous version of the course (56.9%) is more common in PS, while the mixed (27.7%) and episodic (15.4%) variants were less common.

Table 1. The measure of the informativeness of selected positive and negative symptoms in patients with PS in PPP

Symptoms	DC*	KM**
stereotypic thinking	-17,04	4,58
disorganized thinking	-22,42	4,01
passive/apathetic social withdrawal	-16,21	3,86
suspiciousness/persecution	-18,78	3,18
emotional withdrawal	-14,55	2,79

* - diagnostic coefficient;
** - Kullback measure of informativeness.

Table 2. The measure of the informativeness of selected positive and negative symptoms in patients with APPD in PPP

Symptoms	DC*	KM**
unusual thought content	24,35	4,77
hallucinations	25,14	4,54
excitement	15,22	3,91
anxiety	21,11	3,63
tension	13,48	3,10
Poor attention	9,95	2,58

* - diagnostic coefficient;
** - Kullback measure of informativeness.

Table 3. The level of suicidal risk in patients with PS and APPD with different course of PPP

The course of PPP	Level of suicidal risk (M±σ)	
	PS patients	Patients with APPD
Continuous	88.7±25.6	96.1±33.3
Episodic	94.3±26.2	399.4±67.7*
Mixed	278.5±53.9*	101.3±20.9

(differences are statistically significant: * - p<0.01)

Table 4. Distribution of premorbid features of character among patients with PS and APPD

Premorbid character traits	Groups of examinees			
	PS patients (n=65)		APPD patients (n=72)	
	Abs .	%±m	Abs .	%±m
Hyperthymic	7	10.8±1.2	8	11.1±1.4
Emotive	9	13.8±1.6	18	25.0±2.9*
Anxious	6	9.2±1.1	19	26.4±3.0**
Demonstrative	3	4.6±0.7	4	5.6±0.8
Dysthymic	20	30.8±3.1*	12	16.7±2.0
Sticking	25	38.5±3.8**	11	15.3±1.8
Pedantic	17	21.2±2.7	14	19.4±2.2
Cyclothymic	2	3.1±0.6	2	2.8±0.5
Excitable	8	12.3±1.4	10	13.9±1.7
Ecstatic	3	4.6±0.7	10	13.9±1.7**

(differences are statistically significant: * - p<0.05; ** - p<0.01)

Table 5. Average group level of expression of premorbid features of character in patients with PS and APPD

Premorbid character traits	The level of expression M±σ (points)	
	PS patients	Patients with APPD
Hyperthymic	6.5±2.4	6.1±2.1
Emotive	7.2±3.3	13.9±2.5*
Anxious	10.3±4.1	19.3±2.9*
Demonstrative	8.9±2.0	9.4±2.4
Dysthymic	19.6±1.9*	11.1±1.7
Sticking	20.2±3.0**	9.2±2.7
Pedantic	12.2±2.7	11.7±2.5
Cyclothymic	7.7±2.0	17.0±2.3**
Excitable	13.8±2.2*	7.3±1.8
Ecstatic	9.1±2.6	20.3±1.8**

(differences are statistically significant: * - p<0.05; ** - p<0.01)

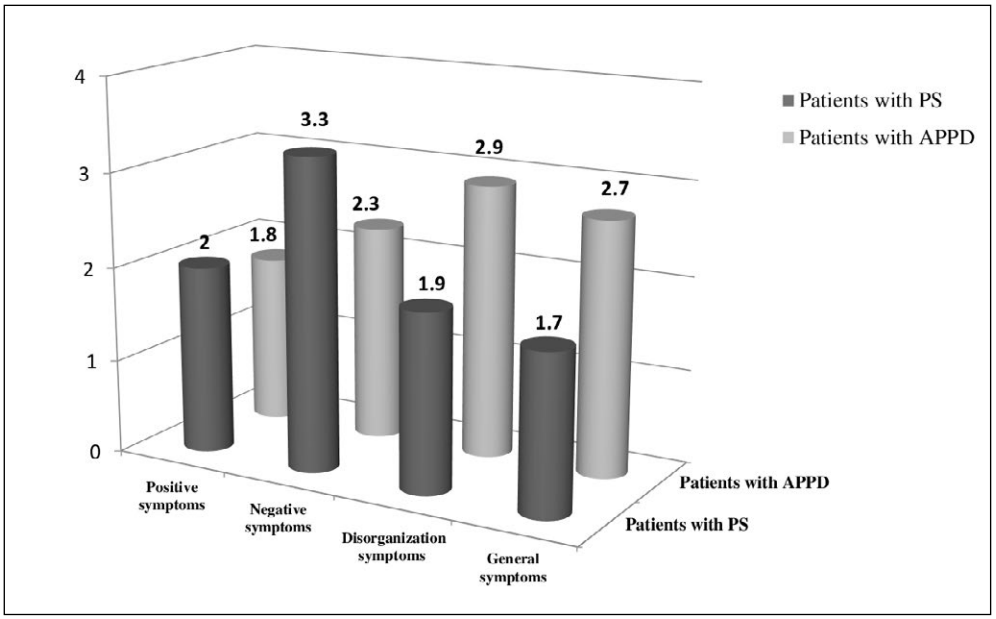

Fig. 1. The degree of severity of groups of symptoms of patients with PS and APPD in the prodromal period

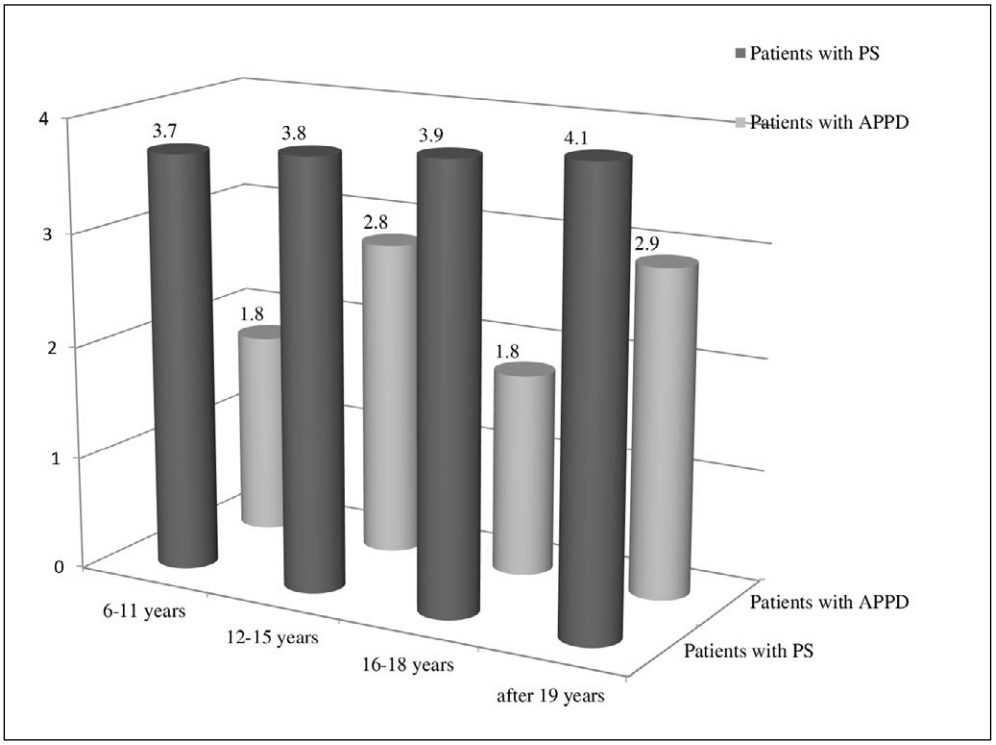

Fig. 2. Dynamics of the level of general social functioning of patients with PS and APPD in PPP at different stages of the patient's life.

In patients with APPD, the predominant variant of the course was mixed (59.7%), continuous (22.2%) and episodic (18.1%) variants were less common. In the process of performing the research, we noticed the relationship between the variant of course of the pathological process and the level of risk of suicidal behavior, which we studied using the scale of the Los Angeles Suicidality Center

The results of this study are presented in Table 3.

It was found that the highest (medium and high) indicators of suicidal risk were observed in patients with APPD with an episodic variant of the course (399.4 points), which occurred in a small number of examined subjects of this group (18.1%).

Among patients with PS, the highest indicators of suicidal risk (278.5 points - the average level) were registered in patients with a mixed version of the course, whose number was 27.7%.

The study of premorbid personality traits of patients with PS and APPD in PPP was carried out with the help of the questionnaire of K. Leongard – Shmishek. Table 4 presents an analysis of the distribution of premorbid character traits among patients with PS and APPD.

Table 5 presents the results of the study of the average group level of the severity of premorbid features of the character of patients with PS and APPD.

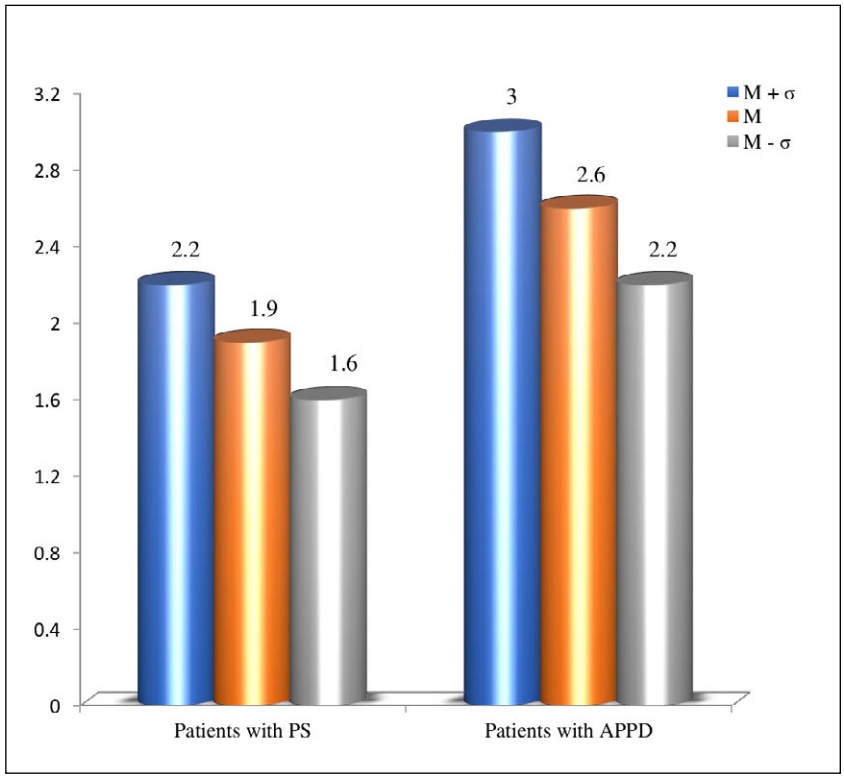

Fig. 3. Correlation of general levels of social frustration in patients with PS and APPD in the prodrome of psychosis

According to the results presented in Table 2, it should be noted that in the group of patients with PS in the PPP, premorbid personality traits predominate in terms of frequency and intensity:

1) accentuated (20.2±3.0 points , at p<0.01) sticking (in 38.5% of cases, p<0.01) personal traits;
2) accentuated (19.6±1.9 points , at p<0.05) dysthymic (in 30.8% of cases, p<0.05) personal traits.

In the group of patients with APPD in the PPP, the predominant (in terms of frequency and intensity) personal traits were:

1) accentuated (19.3±2.9 points, at p<0.05) anxious (in 26.4% of cases, p<0.01) personal traits;
2) emotive (in 25.0% of cases, at p<0.05) personal traits with tendency to accentuation (13.9±2.5 points, p<0.05).
3) ecstatic (in 13.9% of cases, at p<0.01) personal traits with a tendency to accentuation (20.3±1.8 points, p<0.01).

The study of the level of social functioning in PPP in patients with PS and APPD, at different age periods of their life, was conducted with the help of a structured PAS-SI interview, compared with the medical history data.

The dynamics of the level of general social functioning of patients with PS and APPD in PPP, at different stages of the patients' lives, is presented in fig. 2

According to the results presented in fig 3, in all age periods, the average-low level of general social functioning was observed in patients with PS in PPP. Also we notice a gradual slight decrease in this level in the year before the manifestation of psychosis:

1) 6-11 years old - 3.7±0.7 points (p<0.01);
2) 12-15 years old - 3.8±0.5 points (p<0.05);
3) 16-18 years old - 3.9±0.5 points (p<0.01);
4) from 19 years old - 4.1±0.5 points (p<0.05).

Whereas in patients with APPD, wave-like fluctuations in the level of general social functioning were found, from high to medium and from medium to high, with an medium level of general social functioning a year before the manifestation of psychosis:

1) 6-11 years old - 1.8±0.3 points (at p<0.01);
2) 12-15 years old - 2.8±0.3 points (at p<0.05);
3) 16-18 years old - 1.8±0.3 points (at p<0.01);
4) from 19 years old - 2.9±0.4 points (at p<0.05).

Using the method of L.I. Wasserman (modified by V.V. Boyko), the general level of social frustration and the level of frustration according to individual social factors of the life of patients with PS and APPD in the prodrome of psychosis were studied.

A reduced general level of social frustration (1.9±0.3 points, p<0.05) was found in PPS patients.

A moderate general level of social frustration (2.6 ± 0.4 points, p < 0.05) was found in patients with APPD in the prodrome of psychosis

The general level of social frustration in patients with PS in the PPP was lower (1.9±0.3 points, p<0.05) than in patients with APPD (2.6±0.4 points, p<0, 05).

This fact, perhaps, indicates a significant flexibility of adaptation mechanisms in patients with APPD, or the lack of such flexibility in patients with PS.

DISCUSSION

Since the 2000s and up to our time, a lot of scientific research has been conducted with the aim of identifying reliable prodromal symptoms and finding risk factors for the transition of PPP to psychosis. Thus, in the Alison R Yung, Lisa J Phillips research Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group, it was possible to identify such prodromal factors as poor functioning before psychosis, mild psychotic symptoms, depression, and disorganization. Michael T. Compton, MD, MPH; Sandra M. Goulding, MPH; and Elaine F. Walker, PhD report that the most common prodromal symptoms were impaired role function (65.8%), suspiciousness (63.2%), social withdrawal (60.5%), and thinking problems (57.9 %) [11].

Alison R. Yung and Patrick D. McGorry in the article The Initial Prodrome in Psychosis: Descriptive and Qualitative Aspects report on the following predictors of psychosis: Sleep disturbance, Anxiety, Angedirritability, Depressed mood, Deterioration in role functioning, Social withdrawal, Poor concentration, Suspiciousness, Loss of drivel motivation, Perplexity, Low energy/ fatigue, Motor changes, Change in sense of self/ otherdthe world, Perceptual changes [12].

Our work quite accurately repeats and confirms the previous data, since according to our results, the most reliable signs of probable development of psychosis are disorganized thinking, emotional alienation/decreased expression of emotions, suspiciousness, fear of persecution, stereotyped thinking, passive-apathetic social detachment/isolation. However, in our work, we also took into account the heterogeneity of psychoses, and demonstrated the polymorphism of the prodromal picture in different variants of psychosis. We separately distinguished prodromal symptoms of paranoid schizophrenia and non-schizophrenic psychoses (APPD group). In the group of patients with APPD, the most reliable signs of the probable development of psychosis were unusual content of thoughts, tension, anxiety, hallucinatory behavior, impaired attention, agitation, bizarre thinking, reduced tolerance to stress, and sleep disorders [13].

Another important aspect of our research was studying the level of suicidality. According to the results of Ioannis Andriopoulos, 25.5 patients suffering from schizophrenia demonstrate suicidal behavior in the premorbid period. We obtained data that signs of suicidality occurred in 27.7% of schizophrenic patients (with a mixed variant of the course), but for non-schizophrenic psychoses this level was lower (18.1%). We tried to explain these data with a higher level of tolerance to stress, but we got the result that patients from the group of APPD showed a lower tolerance to stress, so this explanation of the lower level of suicidality in this group became impossible. Presumably, the higher level of suicidality in the prodrome of schizophrenia is related specifically to the disorders of thinking and emotions what are typical of this disease or is determined by the lower level of psychological flexibility associated with high indicators of social frustration (according to our results of the analysis of the methodology of L.I. Wasserman (as modified by V.V. Boyko) [14].

It is also important to note the obtained data on the dynamics of changes in the level of social functioning. They were different in the group of patients with schizophrenic and non-schizophrenic psychoses. We found that the level of social functioning was medium-low in patients in the prodrome of paranoid schizophrenia, that is, at the time when the symptoms of mental disorder were only slightly expressed, which calls into question the generally accepted idea that it is the symptoms of schizophrenia that worsen the level of social functioning.

The search for prodromal symptoms is not only a theoretical, but also quite an practical scientific task, as we seek to identify them for the purpose of early intervention or prevention of the development of psychosis. Often, scientific research raises more questions than gives an answers. The results obtained by us and other researchers also present us with a difficult ethical dilemma and raise questions of legality and responsibility. Does the presence of prodromal symptoms make a person sick and, if not, who will be responsible for the prescribed treatment and its possible side effects?

CONCLUSIONS

In this study, we managed to identify the main diagnostically significant prodromal signs of psychosis. Our work demonstrated the difference between the prodromal features of paranoid schizophrenia and other psychotic disorders, indicating that the prodrome of schizophrenia is clinically different from the prodrome of APPD.

We found that the diagnostically valuable signs of the prodrome of paranoid schizophrenia are disorganized thinking of a severe and extreme degree of severity, emotional withdrawal/decreased expression of emotions of moderate severity, suspiciousness, fear of persecution of moderate severity, moderate-severe stereotypic thinking, moderate-severe severity of passive-apathetic social detachment/isolation of medium severity. Diagnostically valuable signs of ADHD were unusual thoughts content of moderate and moderate-severe severity, tension of moderate severity, anxiety of moderate-severe severity, hallucinatory behavior of moderate-severe severity, impaired attention of moderate-severe severity, excitement of

moderate-severe severity, bizarre thinking of moderate severity, reduced tolerance to stress of moderate and severe severity, and sleep disorders of medium severity.

We determined that the level of social functioning in various variants of psychosis decreases even before the appearance of clear psychopathological symptoms, but the depth of decrease in paranoid schizophrenia is more noticeable in comparison with acute polymorphic psychotic disorder.

FUTURE PROSPECTS

The obtained results do not make it possible to accurately predict the development of psychosis, therefore, this issue requires a more in-depth study of the formation factors and risk factors. We see the continuation of our work in a detailed study of correlations between the decrease in social functioning and the symptoms of paranoid schizophrenia and acute polymorphic psychotic disorder.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Dynamics of disability and pain indicators under the influence of physical therapy for adhesives capsulitis and myofascial pain syndrome

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ABSTRACT

Aim: To compare the effectiveness of end-range mobilization and therapeutic exercises, used in combination with ischemic compression, on disability and pain indicators among patients with adhesive capsulitis of the shoulder joint and thoracic myofascial pain syndrome.

Materials and Methods: The study involved 68 patients. Goniometry of the shoulder joint, assessment of pain in myofascial trigger points, and the Shoulder Pain and Disability Index questionnaire were used before and after physical therapy. The duration of physical therapy comprised 3 weeks. Physical therapy of the first group of patients consisted of end-range mobilization and ischemic compression. Patients of the second group performed therapeutic exercises and ischemic compression.

Results: Both groups demonstrated positive dynamics of shoulder joint mobility, Shoulder Pain and Disability Index and pain in trigger points. However, the final results of the studied indicators were better in the first group of patients.

Conclusions: Physical therapy based on the combination of end-range mobilization and ischemic compression had a more positive impact on disability and pain indicators for adhesive capsulitis of the shoulder joint and myofascial pain syndrome as compared to the combination of therapeutic exercises and ischemic compression.

KEY WORDS: musculoskeletal system, manual therapy, mobilization, therapeutic exercises, rehabilitation, recovery

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INTRODUCTION

Adhesive capsulitis of the shoulder joint (ACSJ) occurs in 2-5% of the population [1] and leads to serious functional consequences [2]. This disease is more common for people aged 50 to 55, as well as females [3]. Exact causes of ACSJ are usually unknown. Associations have been found with autoimmune disease states, thyroid disease, diabetes, trauma, neurosurgery, cardiovascular disease, and stroke [4]. The causes of mechanical limitation of movement amplitude in the shoulder joint are thickening, fibrosis and adhesion of the capsule [1]. Stiffness, pain, and deterioration of the shoulder joint function lead to problems with performing basic daily activities [4]. Development timeline of ACSJ is usually divided into 3 phases: freezing, frozen, thawing [3]. Recent scientific works mention permanent disability and constant functional limitations among patients with ACSJ [2].

Myofascial pain syndrome (MPS) is a chronic painful disorder characterized by the existence of trigger points (TPs) [5], excessively irritable spots in strained bands of skeletal muscles. These spots are marked by the presence of pain during the stretch, compression, contraction or overload of the tissue [6], which is often distant from the place of its origin and specific for each muscle [5]. Patients with various pathologies of the musculoskeletal system may have latent TPs [7]. The frequency of MPS reaches 95% in pain treatment centers, and the frequency of latent TPs reaches 55% of young adults without symptoms [8]. Some researchers indicate cases of ignoring MPS by clinicians [6].

The presence of long-term pain in patients with ACSJ and high prevalence of MPS make the problem of physical therapy for patients with ACSJ and MPS highly relevant. However, there are currently no studies focused on the search for the most effective interventions in such patients. Physical therapy plays a key role in the treatment of pathologies of the musculoskeletal system [9, 10, 11]. The effectiveness of various physical therapy interventions is studied in patients with ACSJ

or MPS. In particular, ACSJ treatment involves passive and active therapeutic exercises (stretching, pendulum exercises), cold and heat therapy, proprioceptive neuromuscular facilitation, end-range mobilization (ERM) [12]. TPs are treated with heat, ischemic compression (IC), ultrasound, transcutaneous electrical nerve stimulation, extracorporeal shock wave therapy, and various manual techniques [13].

AIM

The aim of the research was to compare the effectiveness of ERM and therapeutic exercises, used in combination with IC, on disability and pain indicators among patients with ACSJ and thoracic MPS.

MATERIALS AND METHODS

PARTICIPANTS

The study involved 68 patients treated at GI "Institute of Traumatology and Orthopedics of the National Academy of Medical Sciences of Ukraine". Ethical consent was provided by the ethics committee of the local institution (protocol No. 2 dated March 30, 2023) and in accordance with the Helsinki declaration. The patients participated in the study completely of their own free will, which is confirmed by their personally signed informed consents. Each patient was personally informed of their responsibilities and rights as well as the possibility to end the study at any time without any consequences and explaining the reasons for their actions. Inclusion criteria and exclusion criteria are presented in previous scientific works [14]. Before the physical therapy, the patients were consulted by an orthopedist-traumatologist and underwent diagnostic tests. The participants were divided into two groups according to the physical therapy they received.

Methods. The active and passive amplitudes of abduction, flexion and rotations in the shoulder joint were measured in all the patients with the help of goniometer before and after the physical therapy. Goniometry was performed in accordance with the guidelines [15]. The amplitude of rotations was measured in the supine position with the shoulder retracted by 15°. Pain in TPs was assessed when applying 2.5 kg×cm2 pressure (using a digital force gauge VTSYIQI) and the highest score among the studied TPs was registered. The assessment was carried out according to a numerical scale before and after the physical therapy.

Shoulder Pain and Disability Index (SPADI) was also used in the study. This questionnaire is quite popular in orthopedics and physical therapy created to assess shoulder-related pain and disability according to functional results of the patients [16]. The SPADI includes 13 items and two subscales. Each item is assessed on a numerical scale from 0 to 10. Pain subscale includes 5 items. Disability subscale includes 8 items. Both subscales range from 0 to 100 points, which is achieved by converting item scores. The total SPADI score corresponds to the mean value of the subscales. Higher scores in the questionnaire items, subscales or total score correspond to a worse level of functional capabilities, more severe disability and pain.

INTERVENTION

The participants were split up into two groups: the first group (G1, n=34) and the second group (G2, n=34).

While consulting G1 patients, the physical therapist informed them of the specifics of performing ERM and IC (particularly, of pain during the procedures, of the necessity to interact with the physical therapist during mobilization of the joint, as well as of the measures to decrease discomfort during the interventions). ERM procedures were performed 5 times a week (20-25 minutes) in order to improve the range of motion in the shoulder joint. Intensive ERM was used up to and including the V degree. The planned duration of the intervention comprised 3 weeks. A full description of ERM is presented in the previous studies [14]. The physical therapist could slightly increase or decrease the number of ERM procedures. Most of G1 participants (82.4%) received 15 procedures. Other patients received either more or fewer procedures: 2.9% - two procedures fewer; 5.9% - one procedure fewer; 5.9% - one procedure more; 2.9% - two procedures more. Thus, the average duration of the physical therapy in G1 comprised 3 weeks.

At their first consultation, G2 patients received information from the physical therapist of the specifics of the therapeutic exercises and IC, watched a demonstration of the exercises by the specialist and conducted a trial performance of the exercises themselves. The exercises were described and pictured in the information booklet for G2 patients. The patients performed pendulum (from 7 to 10 minutes) and stretching exercises (from 15 to 20 minutes) at home twice a day. They also received two scheduled consultations and a final one. A full description of the therapeutic exercises is presented in the previous studies [17]. The duration of the physical therapy program for G2 patients comprised 3 weeks.

The patients of both groups were advised to perform all activities, including household ones, with the maximum possible range of motion in the shoulder joint.

Table 1. Me (25%;75%) indicators of movement amplitude of the shoulder joint during the first and final assessments, degrees

Movement		First assessment		p*	Final assessment		p*
		G1	G2		G1	G2	
Abduction	passive	58.5 (40; 64.3)	54.5 (46.8; 60)	0.404	125.5 (123.8; 126)	89.5 (85.8; 101.3)	<0.001
	active	55.5 (32; 61.3)	50.5 (42.8; 55.5)	0.364	125 (122.3; 126)	86 (83; 97)	<0.001
Flexion	passive	68 (55.8; 93)	67.5 (53.8; 72)	0.527	180 (180; 180)	130.5 (96; 137.3)	<0.001
	active	63.5 (51; 88)	64 (49; 70.3)	0.667	179 (179; 180)	120 (94; 126.3)	<0.001
Internal rotation	passive	15.5 (14; 20.3)	16 (14.8; 19)	0.975	90 (90; 90)	48 (46; 50)	<0.001
	active	12.5 (10.8; 17.5)	12 (11; 14)	0.868	90 (89; 90)	43.5 (41.8; 45)	<0.001
External rotation	passive	18 (16; 21)	18 (16.8; 20)	0.863	90 (90; 90)	48.5 (46; 50)	<0.001
	active	15 (12.8; 17.3)	14 (12.8; 17)	0.423	90 (89; 90)	45 (43; 46.3)	<0.001

Note. * – Mann-Whitney test.

Table 2. Results of comparing the initial scores of the SPADI items in the groups

	Items	Groups		Criterion*	p
		G1	G2		
1	Pain at its worst	9.5 (8; 10)	10 (8; 10)	-0.617	0.537
2	Pain when lying on the involved side	9.5 (7; 10)	9 (6; 10)	-0.448	0.654
3	Pain when reaching for something on a high shelf	10 (7; 10)	9 (7; 10)	-0.351	0.726
4	Pain when touching the back of your neck	9 (6; 10)	9 (6.75; 10)	-0.172	0.864
5	Pain when pushing with the involved arm	10 (6; 10)	9 (8; 10)	-0.196	0.844
6	Difficulty when washing your hair	8 (6.75; 10)	10 (7; 10)	-0.906	0.365
7	Difficulty when washing your back	10 (8.5; 10)	9 (8; 10)	-0.798	0.425
8	Difficulty when putting on an undershirt or jumper	9 (7; 10)	9 (6; 10)	-0.167	0.868
9	Difficulty when putting on a shirt that buttons down the front	7 (5; 9)	7 (5.75; 9)	-0.509	0.611
10	Difficulty when putting on your pants	5 (4; 8)	7 (4.75; 9)	-1.179	0.238
11	Difficulty when placing an object on a high shelf	10 (7.75; 10)	9.5 (8; 10)	-1.026	0.305
12	Difficulty when carrying a heavy object of 10 pounds (4.5 kilograms)	8 (5; 10)	8 (5; 9)	-0.480	0.632
13	Difficulty when removing something from your back pocket	9 (7; 10)	8 (8; 10)	-0.412	0.681

Note. * – Mann-Whitney test.

For MPS therapy, G1 (in the clinic) and G2 (at home) patients performed IC without any assistance. Individual maps of latent and active TPs were drawn up by the physical therapist and handed out to the patients. Patients of both groups received instructions to perform IC for TPs of various locations. Compression of one point lasted half a minute. The patient could turn around and repeat the compression of the point. IC was performed once a day (15-20 minutes). A full description of IC is presented in the previous studies [14].

STATISTICAL ANALYSIS

SPSS Statistics 21 software was used in the study. Compliance with the law of normal distribution was checked by the Shapiro-Wilk test. Median (Me) and upper and lower quartiles (25%; 75%) of the obtained indicators were calculated since the results of the majority indicators did not conform to the law of normal distribution. The Wilcoxon test was used to compare primary and final results in the group of patients (the software converted the criterion into Z value). G1 and G2 groups were compared by means of the Mann-Whitney test (the software converted the criterion into Z value).

RESULTS

The age of the patients was 53.5 (50; 59) years in G1, and 52 (44.8; 62) years in G2 (Z = -0.559; p=0.576). Duration of symptoms comprised 5 (3, 7) months in G1 and 5.3 (3.4, 7.1) months in G2 (Z = -0.868; p=0.385). There were 26 females in G1 and 23 females in G2 (χ^2 = 0.657; p=0.417). The right upper limb was affected by ACSJ in 15 and 16 patients, respectively (χ^2 = 0.059;

Table 3. Results of comparing the final scores of the SPADI items in the groups

	Items	Groups		Criterion*	p
		G1	G2		
1	Pain at its worst	2 (1; 3)	6 (5; 7)	-6.134	<0.001
2	Pain when lying on the involved side	1.5 (1; 2)	4.5 (4; 5)	-6.305	<0.001
3	Pain when reaching for something on a high shelf	2 (0.8; 2.3)	5 (4; 6.3)	-6.186	<0.001
4	Pain when touching the back of your neck	1 (0; 2)	5 (4; 5)	-5.932	<0.001
5	Pain when pushing with the involved arm	1 (0.75; 2)	5 (4; 6)	-6.083	<0.001
6	Difficulty when washing your hair	1 (0; 2)	6 (4; 7)	-5.625	<0.001
7	Difficulty when washing your back	1 (0; 2)	6.5 (6; 8)	-6.685	<0.001
8	Difficulty when putting on an undershirt or jumper	1 (0; 2)	6 (5; 8)	-6.831	<0.001
9	Difficulty when putting on a shirt that buttons down the front	0 (0; 1)	5 (4.8; 7)	-6.641	<0.001
10	Difficulty when putting on your pants	0 (0; 0)	6 (3; 7)	-6.551	<0.001
11	Difficulty when placing an object on a high shelf	1 (0; 1)	6 (5; 8)	-6.738	<0.001
12	Difficulty when carrying a heavy object of 10 pounds (4.5 kilograms)	1 (0; 2)	5 (3; 7)	-5.830	<0.001
13	Difficulty when removing something from your back pocket	0 (0; 1)	6.5 (5; 7)	-7.140	<0.001

Note. * – Mann-Whitney test

p=0.808). The shoulder joint of the dominant upper limb was affected in 14 patients from G1 and 16 patients from G2 (χ^2 = 0.239; p=0.625).

One patient from G2 had received a steroid injection before consultation with a physician; there were no such patients in G1 (χ^2 = 1.015; p=0.314). One patient from G1 had previously received physical therapy, while G2 had no such patients (χ^2 = 1.015; p=0.314). 32.3% of patients from G1 and 38.2% of patients from G2 received steroid injections after consultation with an orthopedist-traumatologist (χ^2 = 0.258; p=0.612). Two patients from G1 and one patient from G2 took nonsteroidal anti-inflammatory drugs during the course of physical therapy (χ^2 = 0.350; p=0.554).

The results of the first goniometry measurement did not differ in patient groups (Table 1). According to the Wilcoxon test, both groups showed positive dynamics in the mobility of the shoulder joint (p<0.001). The final results were better in G1.

Both groups of patients had similar results of the SPADI items during the first assessment (Table 2). The results of the Pain subscale during the first assessment were 91 (69, 100) points in G1 and 88 (67.5, 100) points in G2 (Z = -0.319; p=0.750). The results of the Disability subscale were 84.4 (65.3; 89.7) points and 82.5 (62.5; 95) points, respectively (Z = -0.325; p=0.745). The total SPADI score was 87.7 (65.1, 94.4) points in G1 and 86.8 (64.5, 96.4) points in G2 (Z = -0.172; p=0.864).

According to the Wilcoxon test, both groups of patients had positive changes in all SPADI items, with the final results being statistically different from the initial ones (p<0.001).

Subscale results and the total SPADI score also improved significantly in both groups of patients. The final statistical results of the Pain subscale decreased to 16 (5.5, 24) points (Z = -5.088; p<0.001) in G1. The results of the Disability subscale decreased to 6.9 (3.1; 15) points (Z = -5.087; p<0.001). The total SPADI score decreased to 10.7 (3; 17.7) points in G1 (Z = -5.087; p<0.001). In G2, the final statistical results of the Pain subscale decreased comparing with the initial ones to 50 (44; 53) points (Z = -5.089; p<0.001). The results of the Disability subscale also decreased to 56.9 (45; 74.1) points (Z = -5.090; p<0.001). The total SPADI score decreased to 52.4 (45.7, 63.8) points in G2 (Z = -5.087; p<0.001).

At the same time, comparison of the final results of the patient groups established statistical differences in all SPADI items according to the results of the final assessment (Table 3). G1 had statistically better results. Accordingly, G1 had better final results of the Pain subscale (Z = -6.409; p<0.001), the Disability subscale (Z = -6.784; p<0.001) and total SPADI score (Z = -6.760; p<0.001) as compared to G2.

Specifics of the changes in the distribution of the total SPADI score in patient groups during both assessments are shown in Fig 1.

Pain in TPs during the first assessment did not differ between patient groups, with Me (25%; 75%) indicators being 9 (9, 9) points in both groups (Z = -0.680; p=0.497). The analysis of the final results revealed better results in G1 (Z = -2.789; p=0.005). Pain in TPs during the final assessment was 3 (3; 4.3) points in G1 patients and 4 (4; 4.3) points in G2. At the same time, both groups had better final indicators than the initial ones (p<0.001).

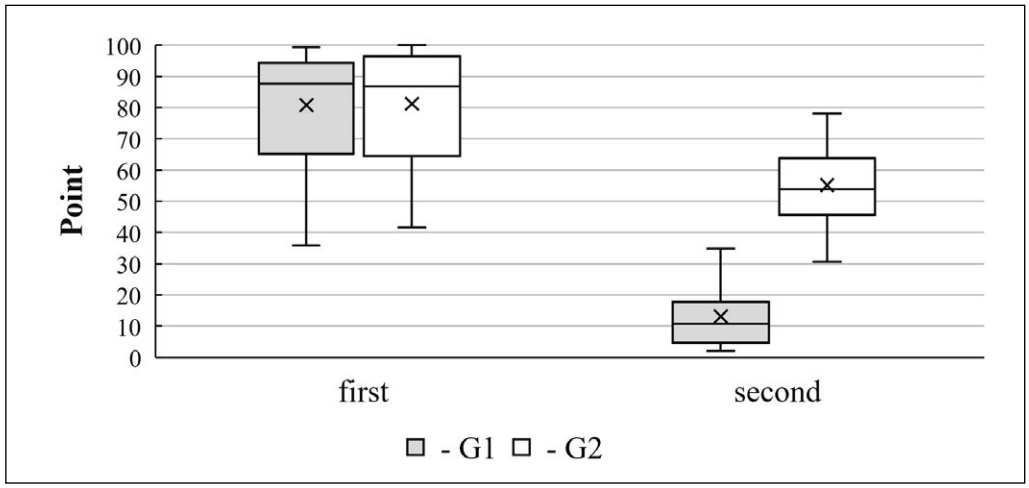

Fig 1. Distribution of the total SPADI score during the first and second assessments in patient groups

DISCUSSION

Both groups had positive dynamics of shoulder joint mobility, SPADI and pain indicators in TPs. However, the use of ERM with IC was more effective as compared to the use of therapeutic exercise with IC. At the same time, it should be noted that the difference in the final indicators of pain in TPs was less significant, which can be hypothetically explained by the influence of two factors: the use of the same MPS therapy in the groups; different dynamics of improving mobility in the shoulder joint and its functional capabilities.

There are no studies comparing the impact of combined physical therapy interventions for patients with ACSJ and thoracic MPS on functional capacity, disability, and pain indicators. However, the impact of shoulder mobilization and therapeutic exercises on pain and disability scores has been studied in patients with ACSJ, and the effectiveness of IC – among patients with MPS.

Having analyzed and compared the effectiveness of passive stretching exercises and mobilization (ERM and scapular mobilization) for ACSJ, S.S. Maarouf et al. [18] established the advantages of mobilization according to the indicators of the SPADI subscales, and the amplitude of movements for flexion and abduction. A. Anitha et al. [19] confirmed the effectiveness of including ERM in the conventional treatment protocol. The researchers found a positive impact on the mobility and scores of the Disabilities of the Arm, Shoulder and Hand questionnaire.

At the same time, the obtained data are consistent with the results of G.Y. Kumar et al. [20], who confirmed the improved dynamics of disability in ACSJ caused by adding mobilizations (3-4 grade) and exercises for scapular stabilization to the ordinary therapy program. The obtained results are consistent with the conclusions of A. Razzaq et al. [21], who indicate the effectiveness of mobilization on disability and joint mobility as compared to the muscle energy technique.

The results of H.A. Qadri [22] also confirmed the effectiveness of ERM on reducing SPADI in patients with ACSJ.

The effectiveness of IC has been studied in many scientific works. For example, one of the recent studies confirmed the effectiveness of IC on improving pressure pain threshold, range of motion, and disability [23]. Another study also confirmed the effectiveness of IC in the therapy of TPs in the sternocleidomastoid muscle according to the indicators of intensity, frequency and duration of headache, pressure pain threshold, and TPs area [24]. Adding IC to TPs therapy improves pain assessment and pressure pain threshold [25].

The obtained results are consistent with the results of the previous studies and complement the findings of the abovementioned scientists regarding the effectiveness of ERM and therapeutic exercises in ACSJ, as well as the effectiveness of IC in TPs therapy among patients with MPS.

CONCLUSIONS

Physical therapy based on the use of ERM and IC had a more positive effect on the indicators of disability and pain in ACSJ and MPS as compared to therapeutic exercises and IC.

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ORIGINAL ARTICLE

CONTENTS

Evaluation of the treatment strategy for complicated allergic rhinitis

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ABSTRACT

Aim: To carry out a comprehensive evaluation of treatment modification for patients with seasonal allergic rhinitis (SAR) complicated by anxiety-neurotic disorders.

Materials and Methods: Patients with SAR in the acute stage on the background of anxiety disorders were studied. Immunological studies were carried out, an assessment of the dynamics of indicators of the quality of life of patients, the level of anxiety / depression was assessed. In the clinical group, a variant of therapy modification was proposed.

Results: Significant changes in the subpopulation ratio of lymphocytes, an increase in the immunoregulatory index, which indicated the severity of the immunological process, were revealed in SAR patients in the acute stage against the background of anxiety disorders. At the same time, a significant activation of the humoral link of immunity was observed: an increase and a significant increase in IgE in the blood serum and an increase in the content of sIgA in the nasal secretion. In most patients, eosinophilia was found in the peripheral blood and in the rhinocytogram before treatment. In the study of the quality of life of patients, changes in many parameters were found.

Conclusions: The combination of "Nazafort Allergy Protection" and Atarax seems to be the most successful, which significantly improved the physical and psycho-emotional state of patients with SAR, complicated by anxiety and neurotic disorders. This combination led to an increase in the stress resistance of patients.

KEY WORDS: seasonal allergic rhinitis, pollinosis, complex therapy of SAR, barrier antiallergic drugs

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INTRODUCTION

In modern world with its rapid development and transformations, climatic and social changes, health care system reforms, one of the global problems remains - allergic diseases, which have a tendency to increase significantly over the last decade [1,2]. Today, according to various data in different countries of the world, frequency of allergic diseases is 25-40% of total population morbidity, and this percentage constantly grows. In some countries, over the past 10 years, number of patients with various forms of allergic reactions has doubled [2-4].

Allergic rhinitis (AR) remains one of the most common diseases in the general structure of allergy pathology. Depending on climate, social and household characteristics of different countries, its prevalence varies in range of 4-32%. Moreover, even mild and short-term symptoms of AR have an undesirable effect on psychological state, disrupt a person's social life, and also limit his professional activity [3,5].

Among ARs, seasonal allergic rhinitis (SAR) or pollinosis has a specific weight. It is characterized by seasonality, symptoms develop at a certain time of the year, which are caused by contact of mucous membrane with plant pollen. Thus, SAR is an allergic disease that is manifested by allergic inflammation of nasal cavity mucous membrane and is caused by an ethiologically significant allergen [2,6]. In climatic zone of central Ukraine, there are three regional peaks of pollinosis symptoms: spring, summer and summer-autumn.

The generally used tactics of SAR treatment include three main components: elimination measures, pharmacotherapy (local and systemic) and antigen-specific immunotherapy (ASIT) [1,3,5,7,8]. In modern allergology, quite a lot of approaches and various recommendations for ASIT and pharmacotherapy have been developed. But pharmacological drugs, along with desired clinical effect, have numerous side effects that limit their use for certain groups of patients. And conducting ASIT is combined with being under the supervision of an allergist, which is not always possible in today conditions. Elimination measures in many program documents, unfortunately, are either insufficient or absent at all. At the same time, elimination of causative factors belongs

to etiopathogenetic treatment methods, especially treatment of allergic diseases. It becomes especially important in cases where patient has serious limitations for pharmacotherapy (pregnancy, childhood, comorbid pathology, old age). But it is almost impossible to limit person's contact with an allergen (plant pollen, household allergens, professional allergens). Therefore, alternative methods of therapy and prevention remain very relevant today for treatment of allergic diseases [8]. The method that would be aimed at creating a barrier and preventing contact, action of the allergen on the mucous membrane targeted, is very relevant for prevention and treatment of SAR.

Among existing modern medical measures for treatment and prevention of SAR, the drug "NAZAFORT allergy protection" (Great Britain) attracts special attention. "Nazafort Allergy Protection" is a spray for local application, which ensures the limitation of nasal mucosa contact with ethiologically significant allergen and prevents development of an allergic reaction, in particular SAR, acting as a barrier to inhaled allergens. Micronized hydroxypropyl methylcellulose reacts with the moist surface of nasal mucous endothelium, where it forms a transparent, gel-like protective barrier that does not interfere with breathing. This prevents mast cell degranulation and the release of immunoglobulin E (IgE) and histamine. As a result, it is possible to avoid an allergic reaction and development of allergic rhinitis symptoms. In addition, with SAR, it is possible to start using "NAZAFORT allergy protection" in advance, 1-2 weeks before expected start of pollination season, or it can be used situationally 15-30 minutes before expected contact with an allergen.

When analyzing literary sources on the effectiveness of "Nazafort protection against allergies", collected data on the dynamics of subjective symptoms in patients with allergic rhinitis is very limited. Decreased release of total IgE and changes in the number of eosinophils in peripheral blood are described, but there is no evidence as laboratory data on the drug effect on local immunity.

On the other hand, it is impossible not to note the psycho-emotional state of a patient with SAR, especially during exacerbation of disease [9,10]. When symptoms of SAR emerge and progress, it very often leads to the development of anxiety, neurotic states in patients, and are most often manifested in emotional lability, reduced concentration of attention, restlessness, anxiety, fear, sometimes obsessive states, very often in the form of migratory itching [11-13]. Thats when the question arises of prescribing additional drugs to combat these conditions [12,14]. From a wide range of sedatives, tranquilizers, anxiolytics, Atarax (hydroxyzine dihydrochloride) (Code: ATX N05B B01) attracts special attention. Which, due to its sedative, tranquilizing and antihistamine properties, is indicated for anxiety states symptomatic treatment in adults and the symptomatic therapy of allergic itching.

AIM

Aim of this study was to carry out a comprehensive evaluation of treatment modification for patients with SAR complicated by anxiety-neurotic disorders.

MATERIALS AND METHODS

The research program included 63 patients with established SAR, persistent, moderate-severe course with clinical manifestations of rhinoconjunctival syndrome, disease course of 2-5 years, with annual exacerbations. All patients have established sensitization to tree, cereal and couch grass pollen, as well as varying degrees of anxiety disorders. 56 patients (89%) complained of periodic, migrating itching that appeares at any time of the day. Age group of patients was 17-50 years. According to the treatment protocol, all patients received intranasal glucocorticosteroids 1 dose in each nasal passage 2 times a day. All patients were divided into 3 groups: 1 group - control (11 patients) received only basic therapy: intranasal glucocorticosteroids and the antihistamine desloratadine; 2nd group - (26 patients) received basic therapy and additionally "NAZAFORT allergy protection" one injection into each nostril 3 times a day; 3rd group - (26 patients) received intranasal glucocorticosteroids, "NAZAFORT allergy protection", and desloratadine was replaced with Atarax 25 mg 2 times a day. Duration of observation was 30 days.

All patients, in addition to general clinical and biochemical studies, were examined by an ENT doctor with X-ray examination of paranasal sinuses, rhinocytogram, nasal peakflowmetry, as well as examination by an ophthalmologist. Immunological and allergological diagnostics were carried out, which included scarification skin tests, the phenotypes of CD4+, CD8+, CD22+ cells and the immunoregulatory index (IRI) of the CD4+/CD8+ ratio [15, 16], general and specific IgE [16,17] and the level of secretory IgA (sIgA) in nasal secretions.

During the entire study, dynamics of patients quality of life indicators were evaluated. To study patients quality of life in different periods: exacerbation of SAR, treatment, rehabilitation using the general questionnaire MOS SF-36 (MOS SF Item Short Form Health Survey). To determine the impact of therapy on patients quality of life, global assessment of the state of treatment quality was performed by doctor and patient. Test results were evaluated according to the point grading system. Pa-

tients independently filled out the SF-36 questionnaire: first, treatment upon admission to the hospital, that is, during the exacerbation phase; at the end of inpatient treatment (on day 12-14); and also for 30 days. The HADS questionnaire and the CES-D self-questionnaire were used to assess the level of anxiety/depression. Severity of the patient's condition was assessed using the Hospital Anxiety and Depression Scale (HADS) [18]. Psychological status was determined on the day of hospitalization and at discharge.

Statistical calculations were performed using the "STATISTICA for Windows 8.0" program package. Non-parametric methods of statistical analysis are applied. The Mann-Whitney test was used to compare quantitative indicators in unrelated groups, and the Wilcoxon test was used in dependent groups. Fisher's test was used to compare the frequencies of a binary feature in two unrelated groups; in cases where the frequencies were less than 10 - criterion 2 with Yates correction. The analysis of the relationship between two traits was carried out by the Spearman method. Differences were considered reliable at a statistical significance level of less than 0.05.

RESULTS

When conducting an allergological examination, sensitization to pollen allergens was established in all patients (100%): tree pollen - 13 patients (20.63%), cereal grass - 9 (14.29%), couch grass - 11 (17.46%), trees and couch grass – 12 (19.05%), cereal and couch grass – 18 (28.57%). The main signs of therapeutic effectiveness were considered to be: positive dynamics of AR course (disappearance of nasal congestion, sneezing, rhinorrhea, mucus running down the back wall of the pharynx, hyperemia and swelling of nasal mucosa according to anterior rhinoscopy). Also, the effectiveness of treatment was determined according to the positive dynamics of clinical and laboratory indicators, which were evaluated on a four-point scale. Treatment quality indicators were: in 1 group (control): excellent result – 2 patients (18.18%), good – 6 (54.55%), unchanged 2 (18.18%), negative – 1 (9.09%); in group 2: excellent - 10 (38.46%), good - 14 (53.85%), unchanged - 2 (7.69%), negative - 0 (0%); in group 3 excellent – 20 (76.92%), good – 5 (19.23%), unchanged – 1 (3.85%), negative – 0 (0%).

Patients of 2nd and 3rd groups noted improvement on the 2nd day of treatment, as nasal congestion and swelling of the mucous membrane decreased. In these groups, on the 10th day of treatment, a full therapeutic effect was achieved, basic therapy was shortened by reducing the frequency of use or completely canceling intranasal glucocorticosteroids. Groups who completely refused intranasal glucocorticosteroids: group 1 - 0 patients (0%), group 2 - 18 (69.23%), group 3 - 20 (76.92%), but continued to use "NAZAFORT allergy protection" for 3 weeks. When comparing clinical courses, it can be noted that in 2nd and 3rd groups the effect came 2 days faster. In control group, 3 patients required additional use of decongestants and antileukotriene drugs.

During a general clinical examination, eosinophilia was detected in peripheral blood in 54 (85.71%) patients, the average rate was 9.26±2.6%. The content of eosinophils in the rhinocytogram was increased in 49 (77.78%) patients, the average content was 8.9±3.5%. It should be noted that after the treatment in group 1, blood eosinophilia and rhinocytogram remained in 3 (27.27%) patients, in group 2 in 9 (34.62%), in group 3 8 (30.77%). Most likely, this is due to the fact that groups 2 and 3 canceled or significantly reduced the intake of intranasal glucocorticosteroids.

During the immunological examination before the treatment, significant changes in the subpopulation ratio of lymphocytes were detected, an increase in CD4+ cells up to 49.39±13.06% was noted; CD8+ decreased to 17.06±9.02% compared to the norm, the average value of the immunoregulatory index (IRI), as one of the key integral indicators of immunity, increased, which indicated the expressiveness of the immunological process. At the same time, a significant activation of the immunity humoral link was observed: an increase in proportion of antibody-producing CD22+ to 40.17±7.62% and a significant increase in IgE in the blood serum to 281.83±98.18 IU/ml, and an increase in the content of sIgA in the nasal secretion to 18.97±4.65 mg/l.

Analysis of changes in immunological parameters in patients before and after treatment showed in the control group: CD4+ from 49.39±13.06 to 42.75±12.94; CD8+ from 18.81±9.63 to 18.21±9.46; IRI from 2.63±0.99 to 2.3±0.93; IgE from 275.73±92.21 to 196.87±97.64; sIgA from 17.83±6.49 to 16.26±5.83, which had no significant changes and only CD22+ significantly decreased from 39.38±12.22 to 25.23±10.86 ($p \leq 0.05$). In group 2, almost all indicators changed reliably: CD4+ from 50.94±12.9 to 39.87±11.18 ($p \leq 0.05$), CD8+ from 17.06±9.02 to 19.82±9, 13 ($p \leq 0.05$), IRI from 2.99±1.21 to 2.01±1.17 ($p \leq 0.05$), CD22+ from 39.5±10.35 to 36.14±11, 88 ($p \leq 0.05$), IgE from 281.83±98.18 to 183.76±83.53 ($p \leq 0.05$), except for the content of sIgA in the nasal secretion from 18.71±7.37 to 15 .43±6.78. We observed a similar pattern in group 3: CD4+ from 50.35±9.86 to 38.95±8.16 ($p \leq 0.05$), CD8+ from 17.23±7.04 to 20.19±4, 15 ($p \leq 0.05$), IRI from 2.92±1.4 to 1.93±1.97 ($p \leq 0.05$), CD22+ from 40.17±7.62 to 36.02±9, 85 ($p \leq 0.05$), IgE from 279.54±84.76 to 187.65±85.38 ($p \leq 0.05$), sIgA in nasal secretion from 18.9±4.65 to 15.38 ±7.12.

When studying patients quality of life, changes in many parameters were found. Thus, in the control group, only the vital activity index (VAI) changed reliably. In clinical group 2, only "NAZAFORT allergy protection" was connected to the treatment, significantly improved indicators of vital activity (VA), physical functioning (PF), general health (GH). However, indicators of the psychological status of patients: manifestation of anxiety (HADS scale, scores), manifestation of depression (HADS scale, scores), manifestation of depression (questionnaire CES-D scores) did not have reliable changes. In the control group, all these indicators also had no significant changes.

In group 3, modification of therapy led not only to a significant improvement in the index of general health (GH), vital activity (VA), role functioning (RF), physical functioning (PF), as well as normalization of mental health (MH), emotional functioning (EF), which led to an increase in stress resistance of patients. Indicators of the psychological status of patients: the manifestation of anxiety, depression according to the scales of specialized questionnaires, also had reliable improvements.

Long-term studies confirmed a steady increase in stress resistance of patients in group 3, which was confirmed by a decrease in the number of manifestations of anxiety.

DISCUSSION

Analysis of treatment modification showed that in groups using "NAZAFORT allergy protection" clinical effect came 2 days faster, a significant number of patients reduced the basic therapy, mainly due to intranasal glucocorticosteroids and continued the use of the drug in complex therapy until the end of the observation.

It should be noted that most patients had eosinophilia in the peripheral blood and in the rhinocytogram before treatment, but after treatment in group 1, eosinophilia persisted in blood and rhinocytogram in fewer patients than in groups 2 and 3, which is most likely due to withdrawal or a significant decrease in use of intranasal glucocorticosteroids.

Before the treatment, significant changes in the subpopulation ratio of lymphocytes were detected: an increase in CD4+ lymphocytes, a decrease in CD8+, an increase in the immunoregulatory index (IRI), as one of the key integral indicators of immunity, which indicated the expressiveness of the immunological process. At the same time, a significant activation of the humoral link of immunity was observed: an increase in CD22+ cells and a significant increase in IgE in the blood serum, and an increase in the content of sIgA in the nasal secretion. As a result of the treatment in the control group with basic therapy, only the number of CD22+ lymphocytes significantly changed, in group 2 and in group 3 with the modification of therapy "NAZAFORT allergy protection" a similar picture was observed, when almost all immunological indicators had reliable positive changes, including IgE in blood serum, except for sIgA in nasal secretions.

In the group with the modification of Atarax treatment, the most pronounced improvement in the psycho-emotional state of patients was observed, the general health, vital activity, role functioning, physical functioning, as well as the normalization of mental health and emotional functioning, which caused an increase in the stress resistance of the patients, significantly improved. Indicators of the psychological status of patients: manifestation of anxiety, depression according to the scales of specialized questionnaires, also had reliable improvements.

Long-term studies confirmed a steady increase in stress resistance of patients in group 3, which was confirmed by a decrease in the number of anxiety manifestations. What was not observed in 1st and 2nd groups.

Thus, modification of the basic therapy of SAR "NAZAFORT allergy protection" led to the modulation of the immune response in the form of a decrease in the allergic reaction, an increase and faster achievement of the clinical effect, and a decrease in the need for the use of inhaled glucocorticosteroids. Although, even though it is effective protection against allergen contact with the shock organ (mucous membrane of the nasal cavity) and can be recommended for use in the treatment of SAR of varying degrees of severity, its separate use does not achieve a sufficient effect on the psycho-emotional state of patients. Therefore, combination "NAZAFORT allergy protection" and Atarax appears to be the most successful, and significantly improving the physical and psychoemotional condition of patients with SAR complicated by anxiety disorders. Such a combination led to an increase in stress resistance of patients.

CONCLUSIONS

Analysis of the modification of the treatment showed that in the groups of application of «Nazafort Allergy Protection» the clinical effect occurred earlier, the basic therapy was reduced due to inhaled glucocorticosteroids. In the groups with the modification of therapy with «Nazafort Allergy Protection», almost all immunological parameters had significant positive changes, with basic therapy, single indicators improved. In the Atarax treatment modification group, the most pronounced improvement in the psycho-emotional state of patients was observed, indicators of the psychological status

had significant positive changes. Long-term studies confirmed a steady increase in the stress resistance of patients, which was confirmed by a decrease in the number of anxiety manifestations. Modification of the basic ATS therapy «Nasafort Allergy Protection» led to the modulation of the immune response and a decrease in the allergic reaction, an increase and a faster achievement of the clinical effect, and a decrease in the need for the use of inhaled glucocorticosteroids. Despite the fact that it is an effective protection against contact of the allergen with the shock organ (nasal mucosa) and can be recommended for use in the treatment of SAR of varying severity, however, its isolated use does not lead to a sufficient positive effect on the psycho-emotional state of patients. Therefore, the combination of «Nazafort Allergy Protection» and Atarax seems to be the most successful, which significantly improved the physical and psycho-emotional state of patients with SAR, complicated by anxiety and neurotic disorders. This combination led to an increase in the stress resistance of patients.

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ORIGINAL ARTICLE

CONTENTS

Reparative osteogenesis in mandible in cases of filling a bone defect with hydroxyapatite-containing osteotropic material and injecting the surrounding soft tissues with thymalin: experimental and morphological study

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ABSTRACT

Aim of the study was to identify the morphological features of reparative osteogenesis in the lower jaw bone of rats in cases of filling a bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin.

Materials and Methods: An experiment was conducted on 48 mature rats of the WAG population weighing 160-180 grams which were divided into four groups. Group 1 included 12 rats with a simulated holey defect in the lower jaw. Group 2 included 12 rats with a simulated holey defect in the lower jaw followed by its closure with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"). Group 3 included 12 rats with a simulated holey defect in the lower jaw with injecting the surrounding soft tissues with thymalin. Group 4 included 12 rats with a simulated holey defect in the lower jaw followed by its closure with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin. The material for the morphological study was a fragment of the lower jaw from the area of the simulated holey defect. Histological, morphometric and statistical research methods were used.

Results: In this study, it was shown by the authors an activation of reparative osteogenesis in the lower jaw under conditions of simultaneous filling the bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injection the surrounding bone defect soft tissue with thymalin. Stimulation of reparative osteogenesis in the lower jaw of rats occurred due to rapid cleaning of the bone defect cavity from necrotic tissues and hematoma fragments; a decrease in the number of neutrophil leukocytes, an increase in the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

Conclusions: Thymalin injection in the soft tissues surrounding the bone defect in the lower jaw, filled with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"), significantly stimulates the process of reparative osteogenesis, which makes it possible to recommend this technique in dentistry for treatment the patients with mandible bone tissue defects.

KEY WORDS: reparative osteogenesis, mandible bone tissue defects, morphology, experiment, hydroxyapatite-containing osteotropic material, thymalin

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INTRODUCTION

The mandible is the strongest and largest bone in the face which plays a central role in function and aesthetics in the oral and maxillofacial region [1]. Mandible bone tissue defects may result from systemic (congenital abnormalities, general diseases, medications) or local (inflammation, tumor, traumatic injuries, such as accidents or dental and surgical treatments) causes [2]. These defects cause severe external deformities and dysfunction in patients due to their special anatomical position, causing facial deformities, seriously reducing their life quality [3].

Trauma is the most common cause of the lower jaw bone injury [4]. When a bone breaks or cracks, the injury is called a fracture [5]. Mandibular fractures are among the most common (60-70%) maxillofacial fractures [6] which have a multi-factorial etiology, such as road traffic accidents, accidental falls, assaults, industrial mishaps, sports injuries, firearm injuries etc. [4].

Treatment of patients with mandible bone tissue defects and reparative osteogenesis stimulation in it is an urgent issue today, despite the large number of invasive and non-invasive treatment approaches and scientific research on this topic [7]. Whilst recent

advances in surgical techniques and biomaterials have improved outcomes of the treatment of mandibular defects, situations still arise when intrinsic regeneration is not possible [8]. The mandible is more difficult to repair than other parts of the bone because of its radians, irregular shapes, dentition and oral function [3]. Treatment measures for this category of patients should be aimed at fully restoring the anatomical integrity and functions of the lower jaw [9, 10]. The latter actualizes the conduct of complex clinical and experimental studies aimed at expanding the arsenal of treatment methods and ways of stimulating reparative osteogenesis.

Our earlier morphological studies of the experimental material proved the activation of reparative osteogenesis in cases of filling a bone defect with a hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and the simultaneous application of electrical stimulation [11, 12]. A promising method of treating patients with mandibular bone defects, from our point of view, may be filling the bone defect with a hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") while simultaneously injecting the surrounding soft tissues with the immunomodulatory drugs, due to immune cells play an important role in reparative osteogenesis [13]. Thymalin can be used as such immunomodulatory drug containing a polypeptide extract of thymus.

AIM

The purpose of the study was to identify the morphological features of reparative osteogenesis in the lower jaw bone of rats in cases of filling a bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injecting the surrounding soft tissues with thymalin.

MATERIALS AND METHODS

An experiment was conducted on 48 mature rats of the WAG population weighing 160-180 grams at the experimental biological clinic of Bogomolets National Medical University. Four groups were formed (Fig. 1).

Group 1 included rats that underwent an incision of the skin, subcutaneous tissue, and superficial fascia in the left submandibular area with a length of 1-1.2 cm and skeletonized a fragment of the outer surface of the branch and body of the lower jaw under ketamine intraperitoneal anesthesia and ultracaine infiltration anesthesia. A ball-shaped drill bit for a straight tip with a diameter of 3 mm with a rotation frequency up to 1000 revolutions per minute was used to form a transcortical hole defect of the body of the lower jaw in the form of a channel, departing from the lower edge of the lower jaw upwards by 2 mm (until the feeling of the bur falling through). The wound was sutured layer by layer with polyamide after the formation of a holey defect.

Group 2 included rats that were modeled with a lower jaw defect similar to group 1. The formed defect was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine), which included hydroxyapatite and β-tricalcium phosphate. The wound was sutured layer by layer with polyamide.

Group 3 included rats that were modeled with a lower jaw defect similar to groups 1 and 2. The wound was sutured layer by layer with polyamide. Thymalin (LLC PP BIOPHARMA, Ukraine) was injected into the soft tissues around the defect for 10 days (0.01 mg/ml per 100 grams of animal weight).

Group 4 included rats that were modeled with a lower jaw defect similar to groups 1-3, which was filled with synthetic bone graft "Biomin GT" (RAPID. Ukraine). The wound was sutured layer by layer with polyamide. Thymalin (0.01 mg/ml per 100 grams of animal weight) was injected into the soft tissues around the defect for 10 days.

In groups 1-4 the animals were removed from the experiment on 3, 7, 14 and 28 days (3 animals for each experimental period).

The material for the morphological study was a fragment of the lower jaw from the area of the simulated holey defect. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours, decalcified and carried out according to the generally accepted method and embedded in paraffin. From paraffin blocks serial sections with a thickness of 4-5 μm were made, which were stained with hematoxylin and eosin, picrofuchsin according to van Gieson.

Examination of the microslides was carried out using a laboratory microscope ZEISS Primostar 3 (Carl Zeiss, Germany) with a built-in color digital camera. Morphometry was carried out using the Labscope program. During a morphometric study, it was determined in the lamellar bone tissue of the regenerate the specific volume of bone trabeculae (%); the specific volume of intertrabecular space (%); the specific volume of intertrabecular space filled with connective tissue (%); the specific volume of intertrabecular space with foci of hematopoiesis (%).

In microslides stained with hematoxylin and eosin in the bone tissue surrounding the holey defect, the brightness coefficient was determined in the Lab color model using the computer program "Analysis of color properties of raster images" [14].

The indicators in the groups were processed statistically using the PAST program (version 4.15, Natural

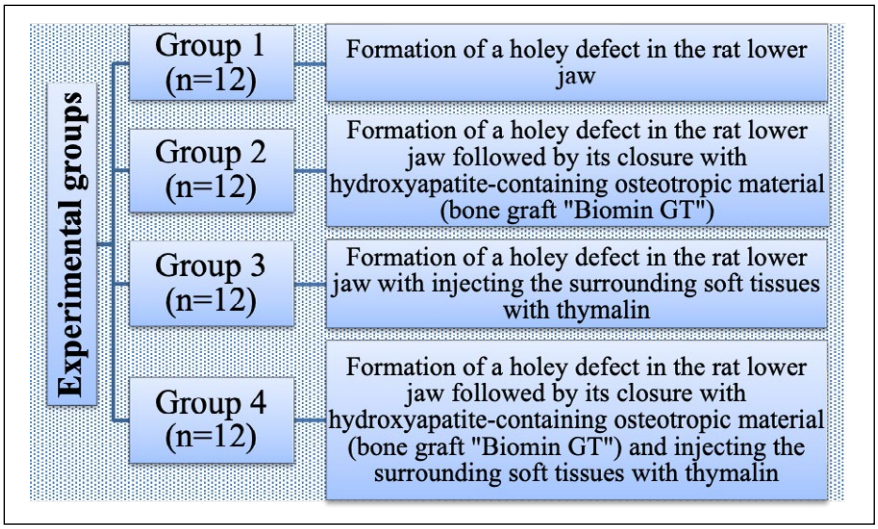

Fig. 1. Characteristics of the experimental groups.

History Museum, University of Oslo, Norway). Mean values of indicators in groups were compared using the Student's t-test and Mann-Whitney U-test. Differences were considered significant at $p<0.05$.

RESULTS

On the 3rd day of the experiment, an extensive defect was revealed in the bone tissue of the lower jaw of rats of groups 1-4, in the lumen of which, among fragments of blood, fragments of stratified squamous epithelium, muscle, connective and bone tissues with dystrophic and necrotic changes were noted. In groups 2 and 4, bone graft granules were identified among necrotic tissues and blood elements. In all groups, alteratively changed epithelial and mesenchymal tissues were diffusely infiltrated with neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, and cells of fibroblastic differon (Fig. 2). Among the polymorphic cellular infiltration, neutrophil leukocytes predominated in groups 1 and 2, and monocytes, macrophages, lymphocytes and fibroblastic cells predominated in groups 3 and 4. In groups 3 and 4, osteoclasts were also identified among the cellular elements, represented by large multinucleated cells, which were often located around alteratively changed fragments of bone tissue. In all groups, foci of immature granulation tissue were identified in the defect cavity, characterized by the presence of many full-blooded capillaries and varying densities of cellular infiltration (Fig. 2). The latter was sparsely cellular in groups 1 and 2, and densely cellular in groups 3 and 4. Granulation tissue in groups 2 and 4 was often localized around bone graft granules.

In the bone tissue surrounding the defect, the edges had unclear outlines with signs of resorption. The latter changes were due to the activation of the morphofunctional state of osteoclasts, which was more pronounced in groups 3 and 4 (Fig. 2). Moderate or pronounced alterative changes were also identified in this tissue, which were manifested by uneven staining of the structures with hematoxylin and eosin. A morphometric study determined the brightness coefficient in bone tissue, which did not differ ($p>0.05$) in groups 1-4 (Table 1). In the periosteum, pronounced dystrophic-necrotic changes, hemodynamic disturbances represented by edema, vascular congestion and hemorrhages were noted. In these tissues, polymorphic cellular infiltration was represented by neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, and cells of fibroblastic differon. Polymorphic cellular infiltration was characterized in groups 1 and 2 by a predominance of neutrophilic leukocytes, and in groups 3 and 4 – monocytes, macrophages, lymphocytes and fibroblastic cells.

On the 7th day of the experiment, compared to the 3rd day, in the lumen of the bone defect the remains of a blood clot, represented by masses of fibrin and hemolyzed erythrocytes with an erased pattern, were noted; the specific volume of alteratively changed tissues decreased. These changes were more pronounced in groups 3 and 4 compared to groups 1 and 2. Alternatively changed tissues, as on the 3rd day of the experiment, were diffusely infiltrated with neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, cells of fibroblastic differon, among which neutrophilic leukocytes predominated in groups 1 and 2, and monocytes, lymphocytes, macrophages, cells of fibroblastic differon – in groups 3 and 4. On the 7th day of the experiment, compared to the 3rd day, in all groups, among the detected infiltration, the number of monocytes, lymphocytes, macrophages, and fibroblastic cells increased. Mature granulation, connective and osteogenic fibroreticular tissues were also detected in the lumen of the bone defect.

Table 1. Average values of the brightness coefficient in the bone tissue surrounding the holey defect in groups 1-4

Group	Day of the experiment			
	3	7	14	28
1 holey defect	0.66±0.009	0.66±0.013	0.63±0.010 [4]	0.59±0.007 [4]
2 holey defect+bone graft "Biomin GT"	0.67±0.009	0.66±0.001	0.64±0.008 [4]	0.59±0.008 [4]
3 holey defect+thymalin	0.66±0.009	0.62±0.015 [1,2,4]	0.58±0.007 [1,2,4]	0.53±0.012 [1,2,4]
4 holey defect+bone graft "Biomin GT"+ thymalin	0.65±0.010	0.61±0.015 [1,2,4]	0.56±0.010 [1,2,4]	0.53±0.008 [1,2,4]

Note: [1] – significance of differences compared to the indicator of group 1; [2] – significance of differences compared to the indicator of group 2; [3] – significance of differences compared to the indicator of group 3; [4] – significance of differences compared to the previous period of the experiment.

In group 3 and, especially, in group 4, compared with groups 1 and 2, there was a higher content of osteogenic fibroreticular tissue. The latter was determined in areas of osteoblasts accumulation in the connective tissue in groups 1-4, and in groups 2-4 also around the bone graft. In single fields of view in group 4, isolated, weakly mineralized bone beams were visible in the connective tissue (Fig. 3).

Alterative changes of varying degrees of severity were identified in the bone tissue that bordered the defect cavity (moderately expressed in groups 3 and 4, pronounced in groups 1 and 2). The brightness coefficient in bone tissue in groups 3 and 4 had a significantly ($p<0.05$) lower value compared to groups 1 and 2, which indicated a greater degree of mineralization of bone tissue (Table 1). The brightness coefficient did not change ($p>0.05$) in groups 1 and 2, but decreased ($p<0.05$) in groups 3 and 4 on the 7th day compared to the 3rd day.

Predominantly in groups 3 and 4 compared to groups 1 and 2, the periosteal and endosteal surfaces of the bone tissue bordering the defect were characterized by a high density of osteogenic cells and their increased proliferative potential with the formation of osteogenic fibroreticular tissue (Fig. 4). The layers of the latter anastomosed with each other, grew towards the defect and filled its lumen.

On the 14th day of the experiment, the regenerate filling the lumen of the bone defect was represented in all groups by granulation tissue of varying degrees of maturity, connective, osteogenic fibroreticular and lamellar bone tissues. Among these tissues in the regenerate, granulation and connective tissues predominated in group 1, osteogenic fibroreticular and lamellar bone tissues predominated in group 2, and lamellar bone tissue predominated in group 3 and, especially, in group 4. In groups 2 and 4, active osteogenesis processes were observed around the bone graft granules, the number of which, compared to day 7, did not change. In some of the visual fields, a connective tissue capsule was formed around the graft granules (Fig. 5). In the capsule, as well as in the tissues surrounding the capsule, cellular infiltration was revealed, represented by lymphocytes, monocytes, macrophages, fibroblastic cells.

In groups 1-4, in lamellar bone tissue, bone trabeculae were characterized by heterogeneous staining with hematoxylin and eosin, which indicated varying degrees of mineralization. The bone trabeculae of the regenerate were stained less intensely with hematoxylin and eosin compared to bone tissue, which was located at a distance from the defect. The decrease in the intensity of staining of the bone trabeculae of the regenerate was more pronounced in group 1 compared to groups 2, 3 and, especially, group 4.

During morphometry, it was noted that in all groups in the lamellar bone tissue of the regenerate, the specific volume of bone trabeculae prevailed ($p<0.05$) compared to the specific volume of the intertrabecular space (Table 2). During survey microscopy, in the intertrabecular spaces, connective tissue with full-blooded vessels or foci of hematopoiesis were identified. It was noted that in all groups the specific volume of intertrabecular spaces filled with connective tissue prevailed ($p<0.05$) compared to the specific volume of intertrabecular spaces with foci of hematopoiesis.

During the analyzing of the obtained indicators, it was noted that the specific volume of bone trabeculae significantly ($p<0.05$) increased from group 1 to group 4, and the specific volume of intertrabecular space decreased significantly ($p<0.05$). The specific volume of intertrabecular space filled with connective tissue and the specific volume of intertrabecular space with the areas of hematopoiesis did not differ significantly ($p>0.05$) in group 1 compared to group 2, in group 3 compared to group 4. However, in groups 3 and 4, compared with groups 1 and 2, the specific volume of intertrabecular space filled with connective tissue and the specific volume of intertrabecular space with the ar-

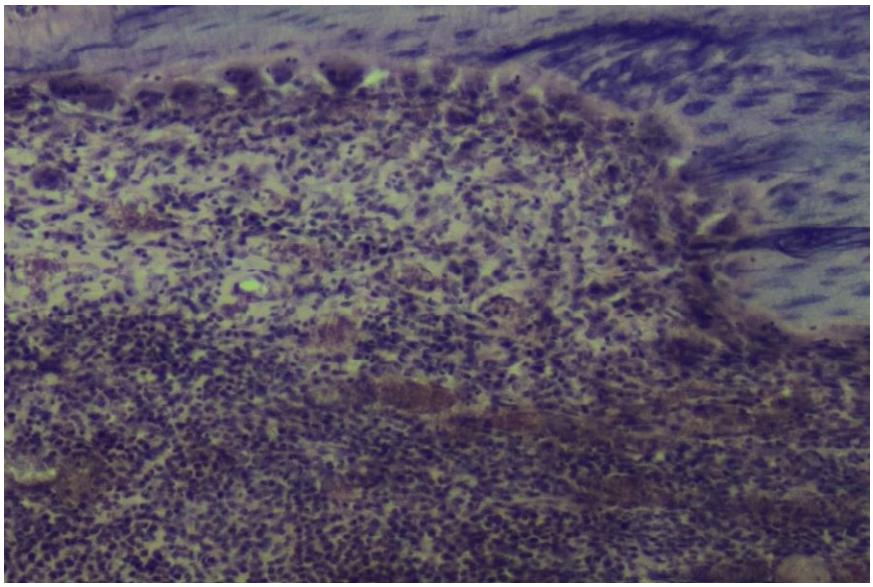

Fig. 2. Group 3. Polymorphic cellular infiltration and immature granulation tissue in the lumen of the bone defect. Resorption by osteoclasts of adjacent to the bone tissue defect. Hematoxylin and eosin staining, ×400.

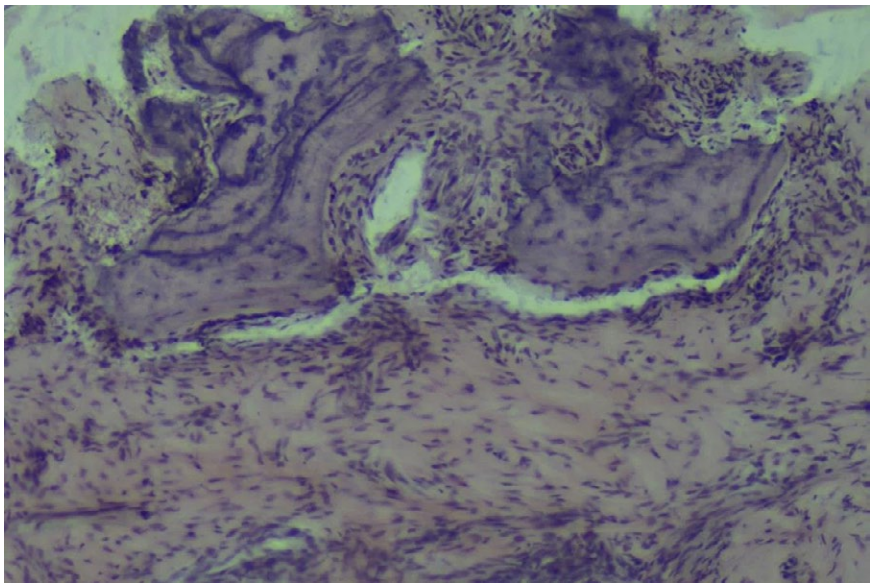

Fig. 3. Group 4. Single, isolated from each other, weakly mineralized bone beams in the connective tissue fields. Hematoxylin and eosin staining, ×400.

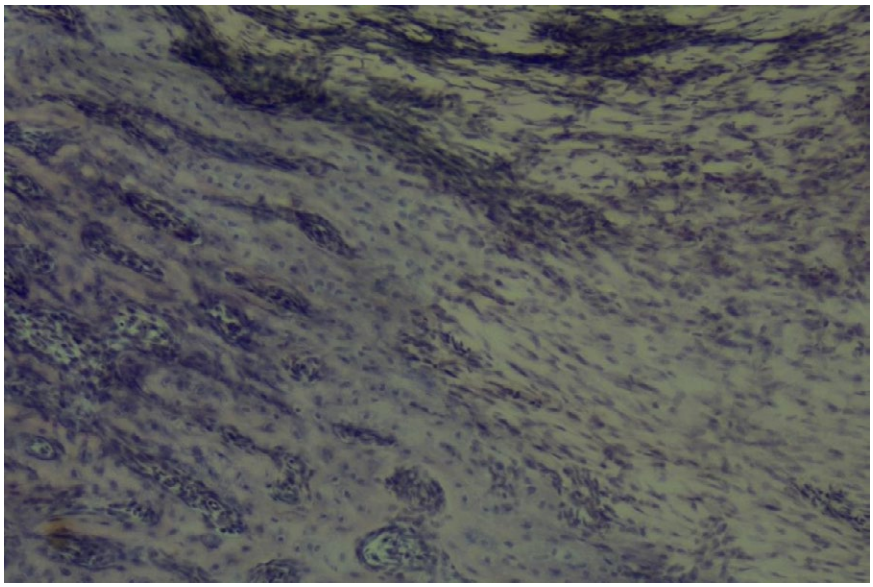

Fig. 4. Group 3. Layers of osteogenic fibroreticular tissue anastomose with each other and fill the lumen of the bone defect. Hematoxylin and eosin staining, ×100.

Table 2. Morphometric study of the lamellar bone tissue from regenerate in groups 1-4

Group	Morphometric indicator	Day of the experiment	
		14	28
1 holey defect	Specific volume of bone trabeculae (%)	54.3±2.05	64.8±2.16
	Specific volume of intertrabecular space (%)	45.8±2.05[1]	35.2±2.16[1]
	Specific volume of intertrabecular space filled with connective tissue (%)	87.1±2.98	75.8±3.41
	Specific volume of intertrabecular space with hematopoiesis foci (%)	12.9±2.98[2]	24.2±3.41[2]
2 holey defect+bone graft "Biomin GT"	Specific volume of bone trabeculae (%)	60.4±2.35[3]	70.5±1.79[3]
	Specific volume of intertrabecular space (%)	39.6±2.35[1,3]	29.5±1.79[1,3]
	Specific volume of intertrabecular space filled with connective tissue (%)	85.4±2.98	74.7±3.12
	Specific volume of intertrabecular space with hematopoiesis foci (%)	14.6±2.98[2]	25.3±3.12[2]
3 holey defect+thymalin	Specific volume of bone trabeculae (%)	66.3±2.51[3,4]	75.8±2.55[3,4]
	Specific volume of intertrabecular space (%)	33.7±2.51[1,3,4]	24.2±2.55[1,3,4]
	Specific volume of intertrabecular space filled with connective tissue (%)	64.9±2.48[3,4]	38.9±2.14[3,4]
	Specific volume of intertrabecular space with hematopoiesis foci (%)	35.1±2.48[2,3,4]	61.1±2.14[2,3,4]
4 holey defect+bone graft "Biomin GT"+ thymalin	Specific volume of bone trabeculae (%)	72.2±2.20[3,4,5]	81.3±2.63[3,4,5]
	Specific volume of intertrabecular space (%)	27.8±2.20[1,3,4,5]	18.7±2.63[1,3,4,5]
	Specific volume of intertrabecular space filled with connective tissue (%)	66.7±2.33[3,4]	37.1±1.99[3,4]
	Specific volume of intertrabecular space with hematopoiesis foci (%)	33.3±2.33[2,3,4]	62.9±1.99[2,3,4]

Note: [1] – significance of differences compared to the specific volume of bone trabeculae; [2] – significance of differences compared to the specific volume of intertrabecular space filled with connective tissue; [3] – significance of differences compared to the indicator of group 1; [4] – significance of differences compared to group 2; [5] – significance of differences compared to the indicator of group 3.

eas of hematopoiesis took on, respectively, significantly ($p<0.05$) smaller and larger values. The morphometric study showed that in group 3 and, especially, in group 4, pronounced processes of reparative osteogenesis and hematopoiesis were observed in comparison with groups 1 and 2.

In the bone tissue that bordered the defect cavity, an active bone formation process was revealed, as evidenced by a pronounced increase in the proliferative potential of osteogenic cells located on the periosteal and endosteal surfaces. These processes were maximally expressed in group 3 and, especially, in group 4 and less pronounced in groups 1 and 2. The brightness coefficient in bone tissue in groups 3 and 4 had a significantly ($p<0.05$) lower value compared to groups 1 and 2 (Table 1). The brightness coefficient on day 14 compared to day 7 significantly ($p<0.05$) decreased in all groups.

On the 28th day of the experiment, the regenerate was represented by connective, osteogenic fibroreticular and lamellar bone tissues. In the direction from group 1 to group 4, the volume of lamellar bone tissue increased (Fig. 6), which indicated an increase in the processes of bone formation. In groups 2 and 4, the number of bone graft granules did not change compared to day 14. The bone beams in lamellar bone tissue in all groups did not have an ordered spatial arrangement and were unevenly stained with hematoxylin and eosin.

In groups 1-4, lamellar bone tissue during a morphometric study was characterized ($p<0.05$) by a predominance of the specific volume of bone trabeculae compared to the specific volume of the intertrabecular space (Table 2). In groups 1 and 2, the specific volume of the intertrabecular space filled with connective tissue was significantly ($p<0.05$) larger compared to the specific volume of the intertrabecular space with areas of hematopoiesis, however, in groups 3 and 4, the specific volume of the intertrabecular space with areas of hematopoiesis was significant ($p<0.05$) greater value compared to the specific volume of the intertrabecular space filled with connective tissue.

The data from the morphometric study indicated pronounced processes of reparative osteogenesis and hematopoiesis in group 3 and, especially, in group 4 compared to groups 1 and 2.

In the bone tissue that bordered the defect filled with regenerate, the brightness coefficient in groups 3 and 4 took on a significantly lower value (Table I) compared to groups 1 and 2. On the 28th day of the experiment, compared with 14 days, the brightness coefficient decreased in all groups (Table I).

DISCUSSION

Our previous studies and the results of numerous studies of various scientists have shown the high efficiency of

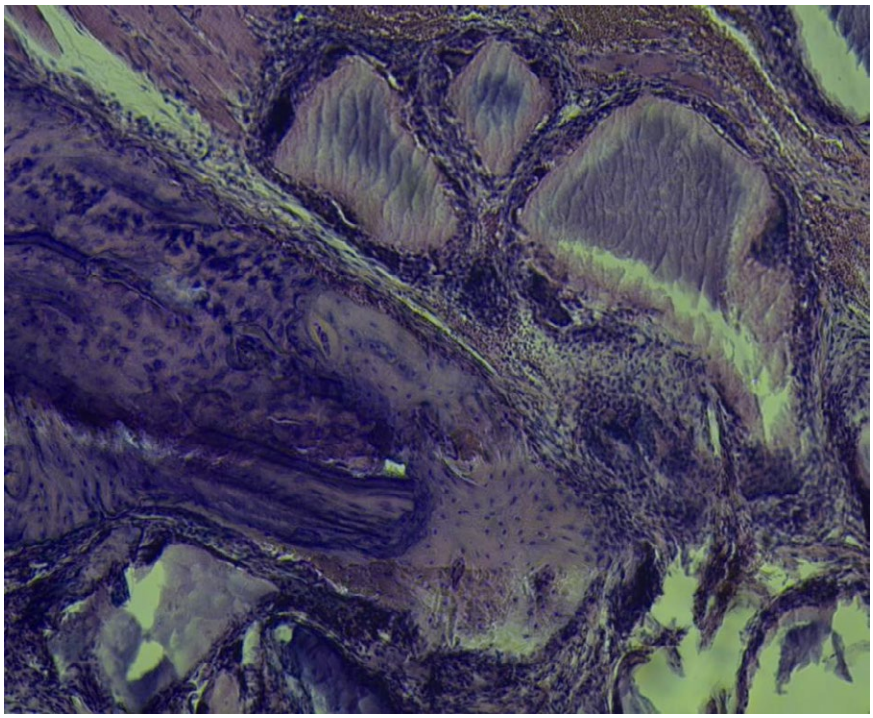

Fig. 5. Group 2. Connective tissue capsule with polymorphic cellular infiltration around the bone graft granule. Hematoxylin and eosin staining, ×400.

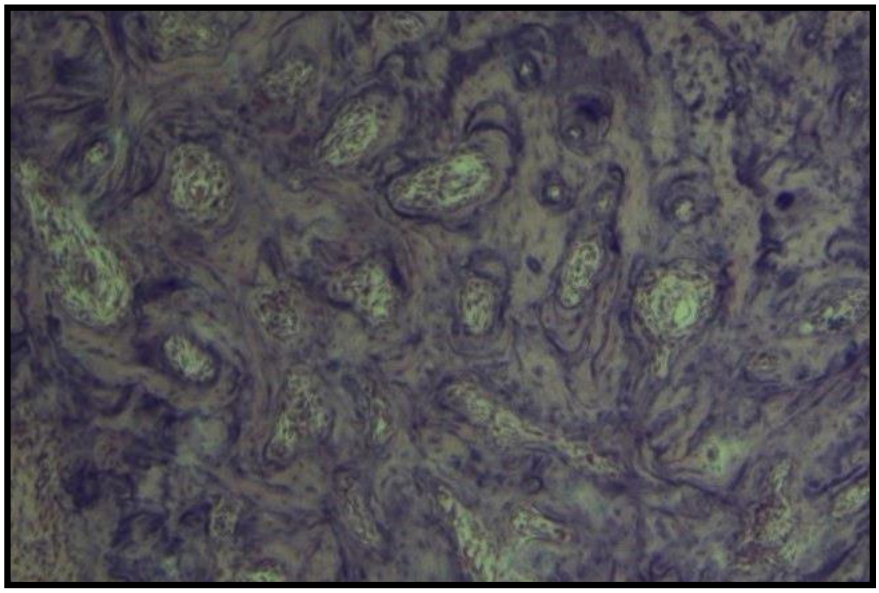

Fig. 6. Group 4. Lamellar bone tissue from the regenerate. Hematoxylin and eosin staining, ×100.

using of various osteotropic materials based on hydroxyapatite to replace the bone defects in the lower jaw [11, 15]. In this study, the authors were the first to show a more pronounced activation of reparative osteogenesis in the lower jaw under conditions of simultaneous filling the bone defect with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT") and injection the surrounding bone defect soft tissue with thymalin.

Bone is considered an osteoimmune system which is based on cooperatively acting bone and immune cells [16]. Dysfunctions of the immune system lead to disturbances in various mechanisms of reparative osteogenesis [17, 18]. Currently, increasing evidence indicates that regulating the immune microenvironment is a promising therapeutic target to promote bone tissue regeneration [19]. We used thymalin as a regulator of local immune reactions in the area of the bone defect.

Thymalin is a polypeptide complex isolated from the thymus which regulates the number and ratio of T- and B-lymphocytes and their subpopulations, stimulates the cellular immunity reactions, enhances the phagocytosis, stimulates the processes of regeneration and hematopoiesis, and improves the processes of cellular metabolism [20].

Our study showed that the injection of thymalin into the soft tissues surrounding the bone defect, which was filled with hydroxyapatite-containing osteotropic

material (bone graft "Biomin GT"), led to rapid cleaning of the bone defect cavity from necrotic tissues and hematoma fragments; a decrease in the number of neutrophil leukocytes, an increase in the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

CONCLUSIONS

Thymalin injection in the soft tissues surrounding the bone defect in the lower jaw, filled with hydroxyapatite-containing osteotropic material (bone graft "Biomin GT"), significantly stimulates the process of reparative osteogenesis, which makes it possible to recommend this technique in dentistry for treatment the patients with mandible bone tissue defects.

Stimulation of reparative osteogenesis in the lower jaw of rats occurs due to the acceleration of the clearance of the bone defect cavity from necrotic tissues and hematoma fragments; reducing the number of neutrophil leukocytes, increasing the number and morphofunctional state of monocytes, macrophages, lymphocytes, cells of fibroblastic differon; balanced change (increase or decrease) in the number and morphofunctional state of bone forming osteoblasts and bone resorbing osteoclasts depending on the stage of reparative osteogenesis; activation of hematopoietic processes in lamellar bone tissue from the regenerate; activation of bone tissue mineralization processes.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Tendencies in disability of the population as a result of malignant neoplasms in Ukraine (on the example of the Poltavia region)

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ABSTRACT

Aim: To study the dynamics of the prevalence and structure of primary disability, including due to cancer, among the population of the Poltava region.

Materials and Methods: The study used a retrospective analysis - the depth of the research search was six years (2019-2023); a comparative analysis - to establish the differences in disability indicators. Determining the trends of disability: analyzing the dynamic series.

Results: The rate of initial disability due to neoplasms (including malignant) for 2019-2023 in Ukraine population is generally stable with a slight downward trend, in the Poltava region, there is a slight downward trend during the years 2019-2021, starting from 2022, begins to increase sharply, while throughout Ukraine the indicator remains stable. Among the able-bodied population of the Poltava region: if until 2021 the picture is identical to the indicators among the adult population, then starting from 2022 the disability of this contingent in the Poltava region begins to increase, while in Ukraine - to decrease. In 2023 among the population of the Poltava region, diseases of the musculoskeletal system became the cause of disability in 20.5 per 10,000 working-age population (I rank place) ; from circulatory system diseases was 12.3 (II rank place); the rate of disability from a neoplasm is 16.1(III rank place).

Conclusions: Analysis of the dynamics and structure of disabling pathology is important and necessary, as it allows to identify diseases that lead to permanent disability, as well as to develop medical and social measures to prevent disability.

KEY WORDS: malignant neoplasms, disability, tendencies

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INTRODUCTION

Malignant neoplasms are a complex, socially significant pathology due to their high rates of morbidity, disability and mortality among the adult population of Ukraine.

About 10 million new patients with various oncological pathologies appear in the world annually. According to the forecasts of the European Parliamentary Commission, by 2030, the number of cancer diseases may increase by another 45% [1-3].

Many studies confirm that cancer is the second most important cause of death in the world [4, 5].

According to the rate of spread of oncological pathology, Ukraine ranks second in the European region. Over the past 10 years, more than 160,000 Ukrainians become cancer patients annually, and about 90,000 die from cancer, including about 30% within a year after establishing of a oncological diagnosis [6].

According to the National Cancer Registry of Ukraine, persons aged 55-74 years dominate the age structure of the incidence of malignant neoplasms in the population of Ukraine. In the structure of mortality from malignant neoplasms at the age of 55-74 years: lung cancer prevailed in men (24.0%), and breast cancer (20.3%) in women. Among the other most frequent oncological causes of death in men of this age were malignant neoplasms of the stomach, prostate gland and colorectal cancer, and in women - malignant tumors of the colon, ovary, uterine body and stomach cancer [7].

With the constant development of medical and preventive technologies, as a result of earlier detection and, accordingly, earlier start of treatment, the survival rate of patients with oncological pathology is increasing [8]. For example, in the United States, the survival rate is 87% among all cancers diagnosed in people aged 50 and older [1]. Patients who have successfully coped with the disease continue to live with the adverse con-

sequences of the disease and anticancer treatment for a long time, and this confirms the need to consider issues regarding the ability of individuals and communities to continue a full quality life.

According to the Law of Ukraine "On the Basics of Social Protection of Persons with Disabilities in Ukraine", a person with a disability is a person with a persistent disorder of the body's functions, which, when interacting with the external environment, can lead to the limitation of his/her life activities, and as a result of which the state is obliged to create conditions for the implementation her rights on an equal basis with other citizens and to ensure her social protection. Disability as a measure of the degree of loss of health is determined by an expert examination in medical and social examination institutions [9, 10].

Nowadays, the medical and social expertise on disability in Ukraine is conducting by medical and social expert commissions. Depending on the degree of the disease, its nosological type and the existing/expected disability group, commissions of a general profile and a specialized profile can be organized.

The medical and social examination system is a set of tools, procedures and measures implemented by state and non-state institutions to assess functioning, vital activities, health and needs for social assistance due to health conditions; causes, time of onset of the disability group; implementation of effective measures for the prevention of disability; rehabilitation of persons with disabilities, their adaptation to social life. Statistical information, which is the basis for planning of rehabilitation measures, for solving social protection issues, etc., plays a big role in solving of such tasks [11].

AIM

The purpose of this work is to study the dynamics of the prevalence and structure of primary disability, including due to cancer, among the population of the Poltava region.

MATERIALS AND METHODS

ACCOUNTING FORMS

In this statistical study, as sources of primary statistical information the following materials were studied: reports on diseases of malignant neoplasms (form No.7) [12]; notification of contingents of patients with malignant neoplasms (form No.35) [13], inspection reports by the medical and social expert commission (form No.157/o) [14].

DATA PROCESSING

The study used a retrospective analysis - the depth of the research search was six years (2019-2023). A comparative analysis was used to establish the differences in disability indicators in the Poltava region in relation to national indicators. Determining the trends of disability was carried out by analyzing the dynamic series, namely the alignment of the dynamic series with the establishment of the rate of increase/decrease. Visibility indicators were used to objectify the changes. All calculations were performed using MS Excel 2016 software package.

RESULTS

The indicator of "primary disability or invalidization" means the frequency of primary disability, i.e. the total number of persons recognized as disabled for the first time in a year. The rate of primary disability in the Poltava region per 10,000 adult population in 2023 was 85.9, against 65.3 in 2022. At the same time, the rate of primary disability in the Poltava region per 10,000 of the relevant population among persons of working age in 2023 was 93.8, against 76.7 in 2022. Probably, the growth of the indicator occurs due to an increase in the number of recognized persons with disabilities of retirement age (indicator among the adult population) and internally displaced persons (indicator among the working age).

Table 1. Indicators of primary disability due to neoplasms (including malignant ones) in the Poltava region and Ukraine for 2019-2023 (per 10,000 adult population)

Years	Primary disability due to neoplasms (with malignant ones)		Primary disability separately due to malignant neoplasms	
	Ukraine	Poltava region	Ukraine	Poltava region
2019	10,2	9,7	9,5	9,3
2020	9,1	9,2	8,5	8,8
2021	9,1	8,9	8,5	8,5
2022	9,2	10,2	8,5	9,7
2023	-	12,9	-	12,4

Table 2. Indicators of primary disability due to neoplasms (including malignant ones) among adults in the Poltava region and Ukraine for 2019-2023 (per 10,000 working-age population)

Years	Primary disability due to neoplasms (with malignant ones)		Primary disability separately due to malignant neoplasms	
	Ukraine	Poltava region	Ukraine	Poltava region
2019	10,6	11,6	9,8	11,1
2020	9,5	10,9	8,9	10,4
2021	9,4	10,8	8,8	10,3
2022	8,9	11,6	8,3	11,0
2023	-	12,3	-	12,3

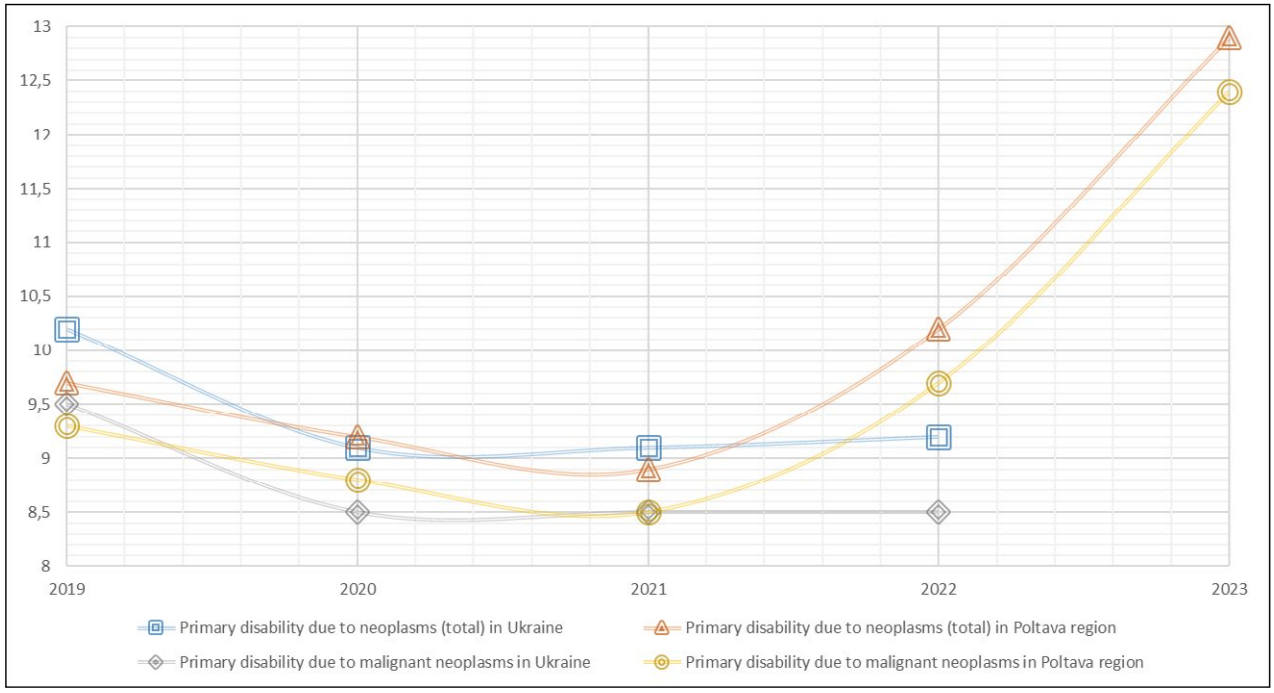

Fig. 1. Dynamics of indicators of primary disability due to neoplasms (including malignant ones) in the Poltava region and Ukraine for 2019-2023.

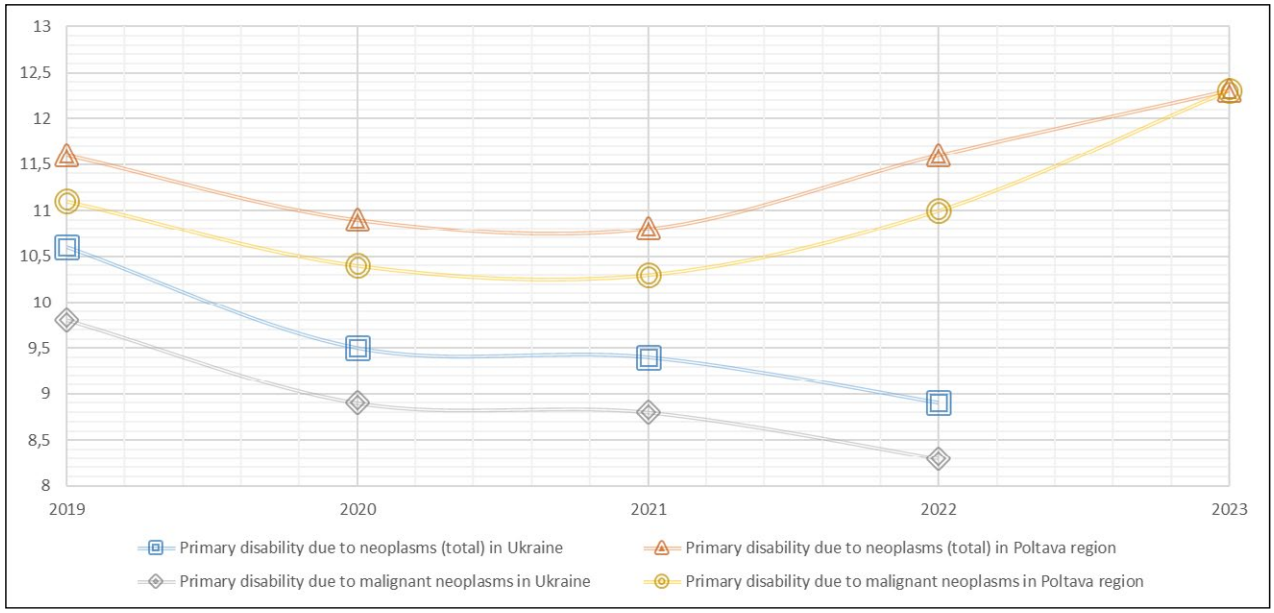

Fig. 2. Dynamics of indicators of primary disability among working-age population due to neoplasms (including malignant ones) in the Poltava region and Ukraine for 2019-2023.

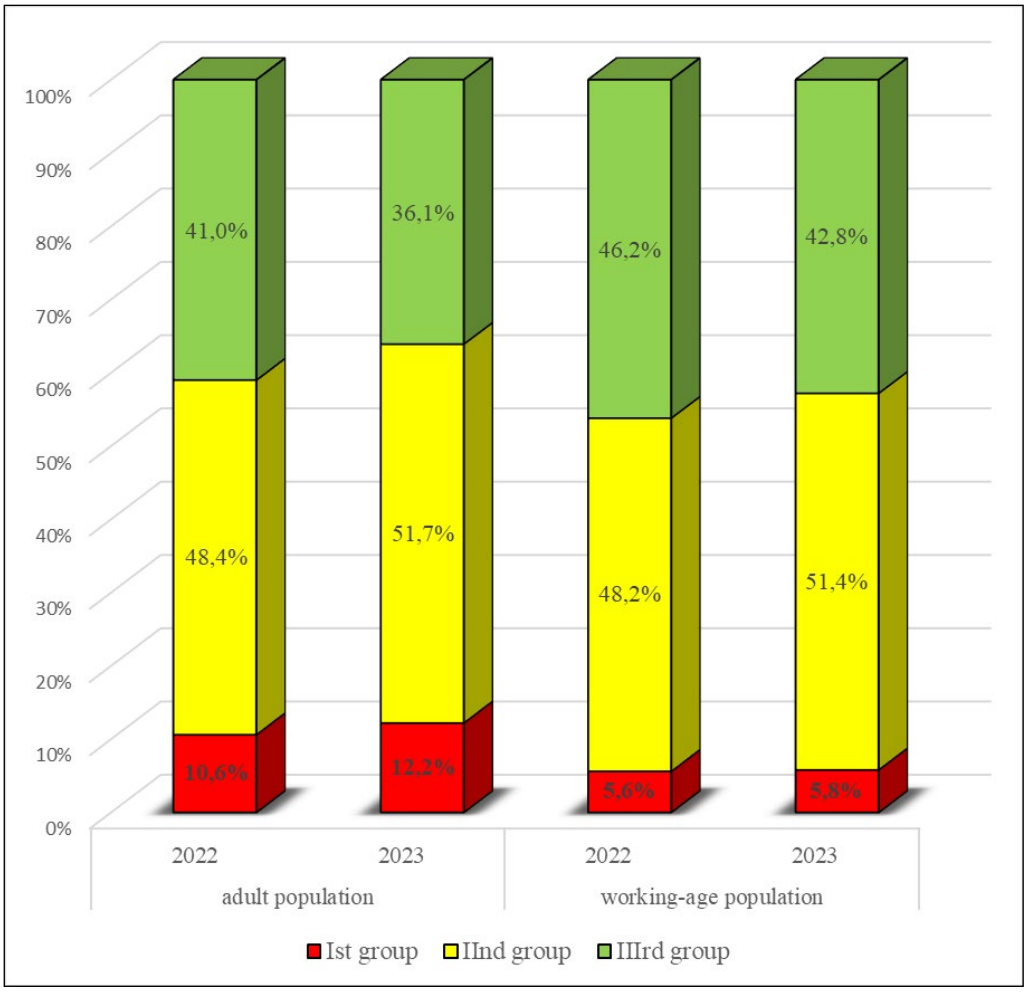

Fig. 3. Structure of primary disability of adults and working-age population of Poltava region in 2022-2023.

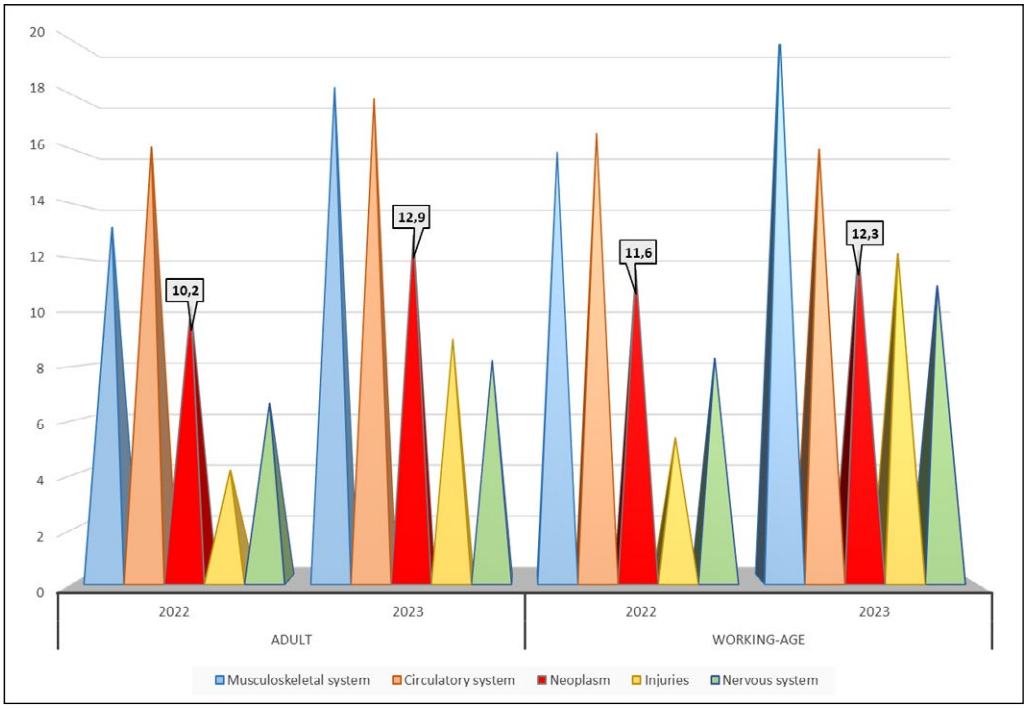

Fig. 4. Nosological structure of primary disability in Poltava region in 2022-2023.

The rate of initial disability due to neoplasms (including malignant) for 2019-2023 in Ukraine both among adults and among the working-age population is generally stable with a slight downward trend (Table 1, 2). As for the situation in the Poltava region, here, both among the adult population and among the able-bodied, there

Table 3. Structure of primary disability according to nosology in Poltava region (rate per 10,000 population)

Rank place	Nosology	2023		2022	
		Adult population	Working-age population	Adult population	Working-age population
1	Diseases of the musculoskeletal system	18,4	20,5	13,2	16,0
2	Diseases of the circulatory system	18,0	16,1	16,2	16,7
3	Neoplasms	12,9	12,3	10,2	11,6
4	Injuries	9,0	12,2	4,1	5,3
5	Diseases of the nervous system	8,2	11,0	6,6	8,3

Table 4. Analysis of the dynamics of the indicator of primary disability in the Poltava region for 2019-2023 (indicator per 10,000 adult population)

Year	Value	Absolute increase (decrease)	Visibility index, %	Growth index (decrease), %	Growth rate (decrease), %	Value by the moving average methodї
Primary disability due to neoplasms (with malignant ones)						
2019	9.7	-	100.0	-	-	9.7
2020	9.2	-0.5	94.8	94.8	-5.2	9.3
2021	8.9	-0.3	91.8	96.7	-3.3	9.4
2022	10.2	1.3	105.2	114.6	14.6	10.7
2023	12.9	2.7	133.0	126.5	26.5	12.6
Primary disability separately due to malignant neoplasms						
2019	9.3	-	100.0	-	-	9.3
2020	8.8	-0.5	94.6	94.6	-5.4	8.9
2021	8.5	-0.3	91.4	96.6	-3.4	9.0
2022	9.7	1.2	104.3	114.1	14.1	10.2
2023	12.4	2.7	133.3	127.8	27.8	12.1

Table 5. Analysis of the dynamics of the indicator of primary disability in the Poltava region for 2019-2023 (indicator per 10,000 working-age population)

Year	Value	Absolute increase (decrease)	Visibility index, %	Growth index (decrease), %	Growth rate (decrease), %	Value by the moving average methodї
Primary disability due to neoplasms (with malignant ones)						
2019	11.6	-	100.0	-	-	11.5
2020	10.9	-0.7	94.0	94.0	-6.0	11.1
2021	10.8	-0.1	93.1	99.1	-0.9	11.1
2022	11.6	0.8	100.0	107.4	7.4	11.6
2023	12.3	0.7	106.0	106.0	6.0	12.3
Primary disability separately due to malignant neoplasms						
2019	11.1	-	100.0	-	-	11.0
2020	10.4	-0.7	93.7	93.7	-6.3	10.6
2021	10.3	-0.1	92.8	99.0	-1.0	10.6
2022	11	0.7	99.1	106.8	6.8	11.2
2023	12.3	1.3	110.8	111.8	11.8	12.2

is a slight downward trend during the years 2019-2021, starting from 2022, the primary disability of the adult population begins to increase sharply, while throughout Ukraine the indicator remains stable (Fig.1). A more interesting picture is observed among the able-bodied population of the Poltava region: if until 2021 the picture is identical to the indicators among the adult population, then starting from 2022 the disability of this contingent in the Poltava region begins to increase, while in Ukraine - to decrease (Fig.2).

As for the distribution of primary disability of the adult population by disability groups, the figures are almost identical to those of previous years. In 2023, among the adult population, the number of persons with disabilities by group was: Ist group – 1,176 people (12.2%), against 775 people (10.6%) in 2022, IInd group – 4,972 people. (51.7%), against 3541 people (48.4%) in 2022, IIIrd group - 3470 people (36.1%), against 2989 people (41.0%) in 2022. In turn, among the working-age population, the number of persons with disabilities in 2023 was: Ist group - 428 people (5.8%), against 335 people (5.6%) in 2022, IInd group - 3761 people (51.4%), against 2882 people (48.2%) in 2022, IIIrd group - 3124 people (42.8%), against 2761 people (46.2%) in 2022 (Fig.3).

The presence of a large number of persons with disabilities, who are assigned to the IIIrd group, implies a high rehabilitation potential and a positive prognosis for rehabilitation.

Regarding the nosological structure of primary disability, in 2023 among the population of the Poltava region, diseases of the musculoskeletal system became the cause of disability in 20.5 per 10,000 working-age population (in 2022 – 16.0) and 18.4 per 10,000 adults population (in 2022 – 13.2); the level of primary disability from circulatory system diseases was 12.3 per 10,000 of the working-age population (11.6 in 2022) and 12.9 per 10,000 of the adult population (in 2022 – 10.2); the rate of disability from a neoplasm is 16.1 per 10,000 working-age population (16.7 in 2022) and 18.0 per 10,000 adult population (16.2 in 2022); disability due to injuries is 12.2 per 10,000 of the working population (5.3 in 2022) and 9.0 per 10,000 among the adult population (4.1 in 2022); disability due to diseases of the nervous system is 11.0 per 10 thousand of the working-age population (in 2022 - 8.3) and 8.2 thousand among the adult population (in 2022 - 6.6) (Table 3).

Statistical data indicate that the rates of primary disability of the working-age population almost always exceed the rates of primary disability among the adult population (Fig.4).

The analysis of the trend of invalidation of the adult population of the Poltava region as a result of neoplasms in general and malignant neoplasms separately indicates significant fluctuations in the indicator from a decrease in 2020 and 2021 to an increase in 2022 and 2023. Thus, compared to 2019, in 2020 the rate of primary disability from neoplasms decreased by 5.2%, and from malignant neoplasms - by 5.4%, in 2021 by 8.2% and 8.6%, respectively. From 2022, there is a sharp increase in both indicators of primary disability: due to neoplasms, the increase compared to 2019 is 33%, and for malignant neoplasms - 33.3% (Table 4).

A practically similar picture is observed when analyzing indicators of primary disability among the able-bodied population, however, the general picture of an increase in the level of indicators in 2023 compared to 2019 is less pronounced: an increase in the indicator of disability due to neoplasms by 6%, and malignant neoplasms by 10.8% is noted (Table 5).

DISCUSSION

As it know, demographic indicators, morbidity and disability indicators are among the main indicators that certify the health of the population. Disability itself, as a statistical indicator, reflects not only the level of health of the population, but also the quality of medical and preventive measures.

O. V. Shirokov [15] indicate a decrease in the level of primary disability in Ukraine in 2018-2020, which coincides with the data for the Poltava region for the corresponding years, however, starting from 2022, an upward trend is observed. This is most likely due to the increase in the population of the region due to internally displaced persons during the Russian-Ukrainian war.

According to S.A. Misyak [16] indicator of primary disability per 10,000 adult population of Ukraine with neoplasms in 2001-2010 ranged from 8.5 to 9.5, that is, it is within the same limits as today. The second indicator that he took into consideration is the share (%) of able-bodied oncology patients who have been assigned a disability group, relative to the total number of persons with disabilities caused by malignant neoplasms. During 2001-2010, this indicator in the Poltava region ranged from 69.0 to 89.0, and in 2019-2023, it was 83.5, respectively; 83.4; 84.8; 79, 2; 66.1. The decrease in 2023 is due, perhaps, to a significant decrease in the number of the working population due to going abroad and participating in hostilities.

Changes in the structure of primary disability among the able-bodied population are interesting. According to available studies [17], in the years 2010-2012, in the Poltava region, diseases of the circulatory system took first place (indicator per 10,000 able-bodied population): in 2010 – 13.2, in 2012 – 11.4 per 10,000 population; the second place is neoplasms: 10.2 and 10.4 per 10,000 population, respectively. Diseases of the musculoskeletal system took third place; the fourth and fifth - injuries and diseases of the nervous system. According to our data, according to similar indicators (per 10,000 working-able population) in Poltava region in 2022, the first place was occupied by diseases of the circulatory system (16.7), the second place by diseases of the musculoskeletal system (16.0), the third place – neoplasms (11.6), and in 2023 the disposition has changed slightly: I place – diseases of the musculoskeletal system (20.5), II place – diseases of the circulatory system (16.1), III place – neoplasms (12,3). As can be seen from the given data, changes occurred both

in the value of the indicators in the direction of increase, and in the value of the share of each nosological group and, accordingly, the ranking place.

CONCLUSIONS

The results of the conducted medical and statistical research indicate an increase in the level of primary disability. Statistical data indicate that the indicators of primary disability of the population of working age almost always exceed the indicators of primary disability among the adult population.

Analysis of the dynamics and structure of disabling pathology is important and necessary, as it allows to identify diseases that lead to permanent disability, as well as to develop medical and social measures to prevent disability.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest.

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REVIEW ARTICLE

CONTENTS

Improving the quality of medical education throught the introduction of moodle system for the formation of terminological competence of medical students

Nadiya O. Fedchyshyn, Anna L. Shkrobot, Nataliia I. Hantimurova, Ivanna I. Vorona, Halyna Ya. Kitura, Larysa Ya. Fedoniuk

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ABSTRACT

Aim is to analyze the possibilities of using the electronic system Moodle for the formation of professional and terminological competence of medical students during the study of terminological competence for improving the quality of medical education.

Materials and Methods: The research used a number of scientific methods: general scientific (analysis, synthesis, generalization), specific research and others which ensured the selection and analysis of the source base, made it possible to determine the general trends in the study of the problem of using the electronic system Moodle for the formation of professional and terminological competence of medical students during the study of terminological competence for improving the quality of medical education.

Conclusions: At I. Horbachevsky Ternopil National Medical University we actively use the e-learning system Moodle (Modular Object Oriented Distance Learning Environment), to which there is free and unrestricted access. Using this program, the student takes on the role of an active subject who independently acquires knowledge, forms his/her own system of skills, of course with the help of certain sources, and the role of the teacher in this scheme is to motivate and support learners, prepare information sources used in self-study, etc. This is due to a significant increase in the requirements for quality training of future specialists in the medical field and market conditions in Ukraine, which set before the higher school the task of training specialists of the new generation who would be highly qualified, competitive, literate, and have perfect command of their professional terminology.

The Moodle system is able to optimize the learning process, promote the formation of terminological competence and master professional vocabulary. When creating educational and methodological complexes for the formation of terminological competence, the means of teaching, as well as the ways of presenting educational material and the principles of organizing the educational activities of students become important. The electronic platform Moodle, which has a wide range of resources for teaching and testing, is able to expand the communicative competencies and skills of students needed to effectively master professional Latin terminology. The Moodle system has the optimal set of resource opportunities for the implementation of blended learning – classroom and extracurricular, which is its main advantage.

KEY WORDS: quality of medical education, health care, medical students, professional competence. distance learning, e-learning platform, Moodle

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INTRODUCTION

Ensuring the competitiveness of graduates of higher medical institutions in the Ukrainian and international labor markets is possible only due to the increase in quality of training of medical and pharmaceutical personnel. Today, a competent approach is relevant in the field of medical education, which is aimed at the transition from theoretical knowledge to professional competence [1]. The formation of professional competence of medical students is carried out by the staff of all disciplines of the curriculum, divided into different cycles. In particular, the system of training specialists in the field of medicine provides for the study of medical terminology during the Latin language classes that has a high professional significance.

Acquiring terminological competence for future physicians is a priority, as long as the fluency in terminology is a condition for further successful professional communication. Fluency in terminology testifies to the knowledge and understanding of professional concepts and phenomena, is an indicator of the culture of professional speech of a specialist, the condition for his/her professional growth [2, 3].

Modern education needs to update the training of specialists, in which they will be able to develop and improve their knowledge and form terminological competence through distance learning and electronic learning platforms. The implementation of distance learning for students can occur mainly with the operation and support of the e-learning platform Moodle [4; 5]. This

software is built in accordance with the standards of information educational systems, provides access to the many resources needed by the student to study the necessary information, allowing the teacher to input materials of any complexity into the system.

THE ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

D. Bobova, L. Viktorova, Z. Gyrych, N. Holub, H. Onufrienko, I. Drozdova, M. Guts, and Ya. Yanush dealt with the issue of the formation of terminological competence. Methodical principles of work on mastering the terms are covered in the researches of M. Baranov, O. Horoshkina, T. Donchenko, A. Nikitina, M. Pentyliuk.

The issue of using the Moodle system is very relevant, especially during the active implementation of distance learning. The system of distance education based on the Moodle platform was created on the basis of socially constructive pedagogy, which today attracts the attention of many researchers and university teachers, such as B. Demyda, N. Fedchyshyn, S. Sahaidak, S. Sysoyeva, K. Osadcha, V. Vysochanskyi, L. Klakovych, P. Kushchak and others.

UNRESOLVED ASPECTS OF THE PROBLEM

In our article, the emphasis is made on the process of studying medical terms for medical students using the Moodle platform. The direct electronic environment gives them the opportunity to form their professional and terminological competence. The teacher has the opportunity to observe the learning process and control it.

Most scholars consider various aspects of the problem of using the latest innovative technologies in the educational process, noting the increasing role of e-learning means at all stages of the educational process, but the possibilities of the use of the electronic platform Moodle in the process of formation of professional terminology competence in Latin is insufficiently studied and therefore determines the relevance of the selected topic.

AIM

The aim is to analyze the possibilities of using the electronic system Moodle for the formation of professional and terminological competence of medical students during the study of terminological competence for improving the quality of medical education.

MATERIALS AND METHODS

The research used a number of scientific methods: general scientific (analysis, synthesis, generalization), specific research and others which ensured the selection and analysis of the source base, made it possible to determine the general trends in the study of the problem of using the electronic system Moodle for the formation of professional and terminological competence of medical students during the study of terminological competence for improving the quality of medical education.

REVIEW

The issues of professional training of a specialist who has perfect professional knowledge, skills and abilities are becoming important. One of the aspects of professional competence of medical students is the study of professional medical terminology [3]. Medical students must acquire such a set of qualities during their studies, thanks to which they will be able to become real professionals. To meet the professional needs and ensure the proper culture of professional communication, the future specialist in the medical field needs to adopt a lot of new terms. Fluency in the professional terminology is an indicator of thorough training of a specialist. Poor knowledge of medical terms causes students' inability to adequately perceive and properly handle special medical literature. An important condition for the successful study and mastering of the disciplines of the medical profile and the students' gaining general professional training is their formation of terminological competence at the lessons of Latin [4].

L. Viktorova notes that being terminologically competent presupposes the ability of a specialist to use the terms accurately and correctly in professional communication [5, p. 166]. Terminological competence is the ability of a specialist to demonstrate proper personal qualities in the situations of professional communication by mobilizing the knowledge of professional terminology.

With the mastery of professional speech by a specialist, the construction of a system of general and professional knowledge begins. To be fluent in oral and written forms of professional communication, medical workers must have a considerable lexical stock of the professional terminology. Assimilation of the language of the profession, and hence the formation of worldview and professional competence of future specialists begins in higher educational institutions. Students have high requirements, which are not only in the advanced knowledge of the profession, but also in a high level of mastery of medical terminology and its fluent use in professional activity. The ability to communicate in the language of the profession promotes the rapid mastery of special

disciplines, increases the efficiency of work, and helps to establish business contacts [6].

Mastering any profession takes place in the process of successive mastering of professional language, including the system of special concepts and terms that form its basis. The specificity of medical terminology lies in the centuries-old use of Latin and terms in the professional activity not only of medical professionals, but also of scientists of all fields of knowledge. The importance of Latin medical terminology in the formation of terminological competence in medical professionals is undoubtedly extremely important, because it is from its mastery that the professional education of the future physician begins. Knowledge of the basics of Latin grammar, special vocabulary and basic Greek-Latin vocabulary provides terminological competence of a specialist and at the same time it significantly increases his/her general cultural level. A well-founded study of medical terminology helps to master the concepts used in the professional activity of the future doctor and provide for his/her proper literacy. Conscious assimilation of terms, selection of word-forming morphemes in them and understanding of their meanings give an opportunity to memorize terms and explain the meaning of unfamiliar words by using the knowledge of basic elements of terms.

Terminological competence is based on Latin language classes, which are part of the integrated process of teaching future physicians. As you know, ancient Greek and Latin are the main international sources for the formation of new terms in all fields of medicine and biology. Knowledge of terms of Greek and/or Latin origin, the basics of Latin grammar helps students in reading medical literature and studying special subjects.

We must not ignore the fact that the modern system of higher medical education involves the active use of information base available only through the Internet. The ability to understand information on special Internet sites, which tell about the latest advances in medicine, new methods of treatment of various diseases, directly depends on the level of terminological competence of future health professionals. The ability to independently form terminological combinations provides adequate entry into the socially significant space of communication and increases the professional culture of the specialist.

The formation of terminological competence of the future physician is a systematic, well-organized and purposeful work related to all sections and topics of the courses "Latin" and "Latin and medical terminology" in combination with the study of other disciplines taught in higher medical institutions.

USE OF ELECTRONIC SYSTEM MOODLE FOR FORMATION OF TERMINOLOGICAL COMPETENCE

Modern teaching materials in Latin for the study of professional vocabulary are designed to have a positive motivating effect on those who learn the language and at the same time create conditions for those who are taught to perform tasks and exercises freely and confidently. Achieving this goal is possible due to the novelty and variety of the proposed material, attractive content and interesting presentation of the material, including modern topics, fascinating stories, problems and illustrations. In recent years, training in the world is increasingly taking place not only in class, but in combination with distance education. Therefore, teachers must use a variety of information technologies to teach their disciplines, because the informatization of education greatly simplifies organizational, educational and other activities and opens a wide range of new opportunities in education. V. Bykov notes that the penetration of information and communication technologies in the educational process creates preconditions for radical renewal of both content-target and technological aspects of education, which is manifested in significant enrichment of didactic methods, teaching aids and on this basis the formation of non-traditional pedagogical technologies based on the use of computers [6]. Thanks to the latest technologies, the role, method, speed and efficiency of using information in the learning process are changing. Thanks to the means of communication it is possible to obtain information and knowledge at a distance. The learning environment can no longer be characterized according to the traditional scheme, when its participants are either a teacher and a student, or a teacher and a group of students. The number of participants in a particular educational process becomes potentially unlimited [7].

DISCUSSION

At I. Horbachevsky Ternopil National Medical University we actively use the e-learning system Moodle (Modular Object Oriented Distance Learning Environment), to which there is free and unrestricted access. Using this program, the student takes on the role of an active subject who independently acquires knowledge, forms his/her own system of skills, of course with the help of certain sources, and the role of the teacher in this scheme is to motivate and support learners, prepare information sources used in self-study, etc. [8].

The Moodle e-learning system provides students and teachers of Latin with a wide range of didactic opportunities to use a variety of educational and meth-

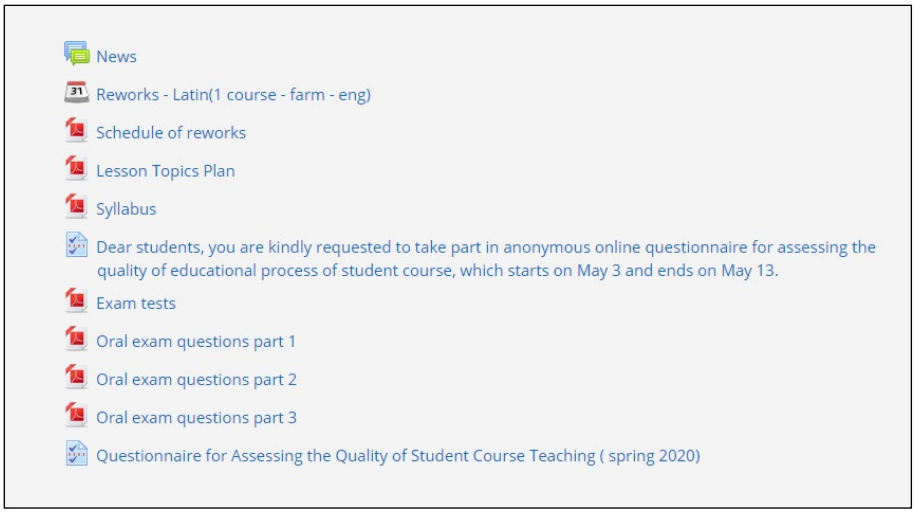

Fig.1. Content of the Latin language course.

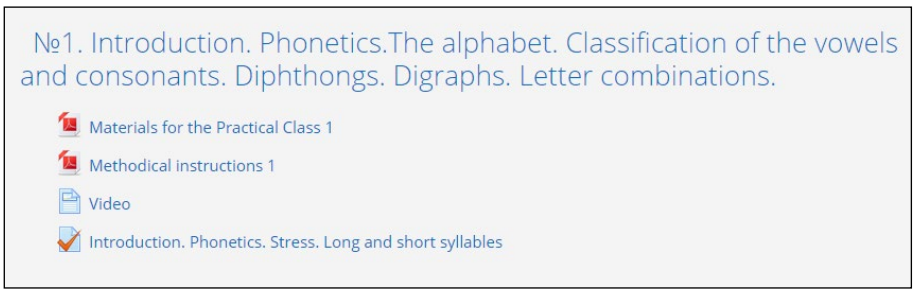

Fig.2. Sample structure of the module of activity "Lesson"

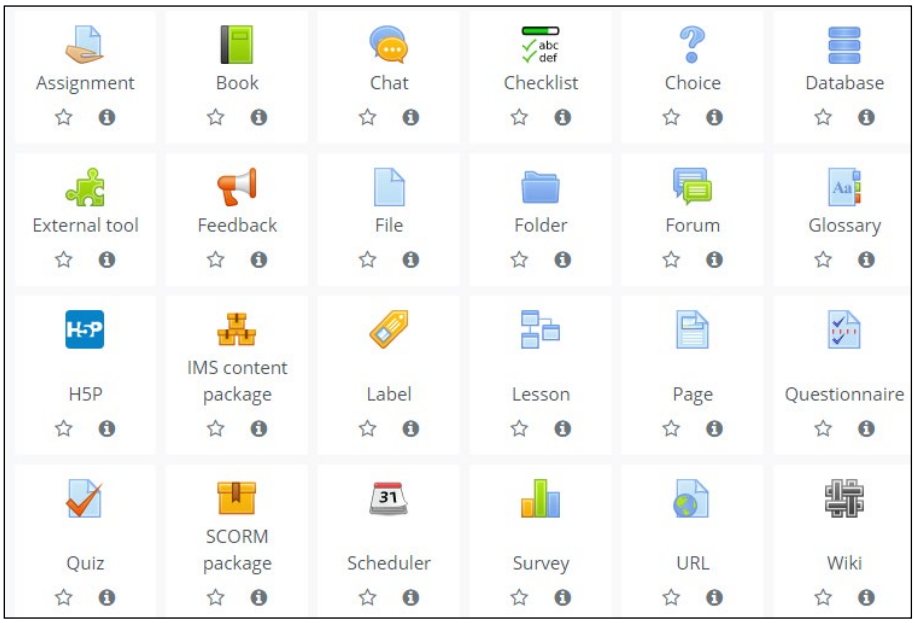

Fig. 3. Tools for learning new terms and communicating with the teacher

odological materials for the formation of terminological competence.

The development of teaching materials in Latin in the electronic educational environment Moodle expands the pedagogical capabilities of the teacher, allowing flexible use of author's materials in Latin to achieve the goals of the educational program. Access to the educational and methodical materials in the electronic environment provides the student with an opportunity to independently plan and manage the educational activity according to individual needs and the chosen trajectory of studying of Latin medical terminology.

With the help of the Moodle system, each teacher has the opportunity to create their own course of the subject. In this course, the teacher provides all the necessary information, distributes a large list of links for a particular module with subheadings or pictures; shows embedded audio or video files directly on the course page; attaches instructions and a brief description of the content of the course section [9].

Fig. 4. Sample image attached to the dictionary article of the glossary "mandibula"

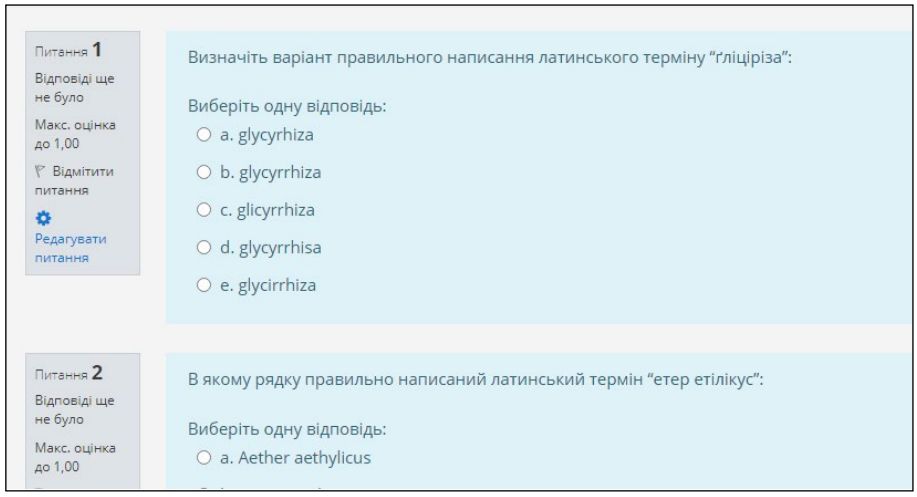

Fig. 5. Sample test for final control

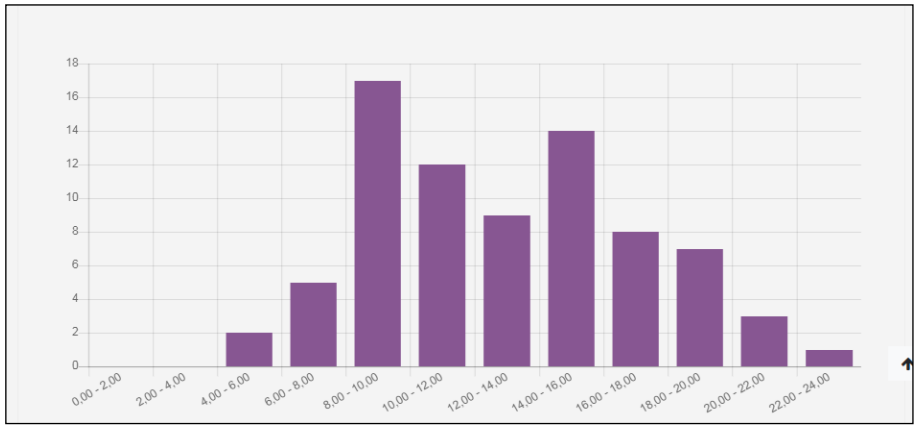

Fig. 6. Range of assessment of the total number of students

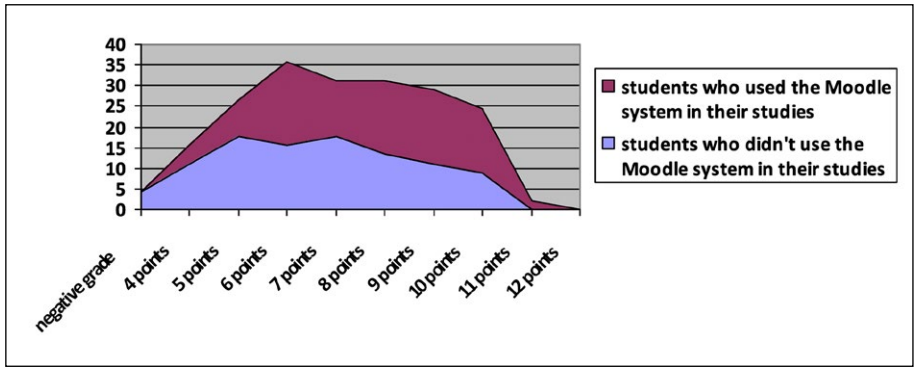

Fig. 7. Comparative diagram of students' progress

The Moodle system offers a variety of ways to provide learning material, test knowledge and monitor performance. For medical students studying Latin, this program will be useful in learning new professional terminology and developing reading and writing skills, in particular, it is advisable to upload additional exercises for better learning, grammar and lexical tests, as well as texts for reading.

For example, starting to study pharmaceutical terminology, first-year students of the Faculty of Pharmacy in the relevant course "Latin" can first get acquainted with the work program of the subject, thematic lesson plans, sample tests for the exam at the end of the subject (Fig. 1).

The whole course is divided into "Classes" or "Topics". The Lesson activity module allows the teacher to present the study material and practical learning activities in interesting and flexible ways. The structure of each topic includes materials for practical classes, guidelines, links to videos and tests for final control (Fig. 2).

The versatility of the platform allows to provide a full range for student self-education and the formation of terminological competence both in classrooms and remotely. After all, the teacher can teach all the additional materials, add video and audio materials with the presentation of the most necessary medical terms and their explanation https://moodle.tdmu.edu.ua/mod/page/view.php?id=148549.

The main tools that allow learners to communicate with each other are as follows: a forum (common to all learners on the main page of the platform, as well as various private forums); Email; exchange of attached files with the teacher; chat; exchange of personal messages (Fig. 3).

The Glossary module allows participants to create and maintain a list of terms and their definitions in the form of a dictionary, collect and organize resources or information data. The teacher can allow the addition of files that will be attached to dictionary entries in the glossary. Attached images are shown in the dictionary article (Fig. 4). Glossary articles can be viewed alphabetically, by section, by date or by author. Dictionary articles can be approved by default before being shown to everyone and do not require teacher approval. The teacher can allow the addition of comments to dictionary articles [10].

The Moodle learning environment includes tools for managing, self-learning, communicating, and assessing student learning. Thanks to the platform, the teacher can remotely control the educational process of students both individually and collectively [11, p. 100]. The Moodle system has certain advantages of using it for evaluation, because as a result of performing certain activities, the result of this performance is evaluated, rather than the student as a person. Besides, penetration of elements of subjectivism into the evaluation is made impossible.

For example, the use of the task "Test" is widespread when completing a block of one topic or several topics (Fig. 5). The test consists of various questions selected from the database of questions: with one answer, many options or the ability to enter your own option [12]. It is very easy for a teacher to summarize and evaluate a student without spending time at the lesson or during distance learning. Computer testing is one of the most effective means of control in learning. Testing as a method of pedagogical measurement consists in quantitative measurement of the level of knowledge, skills, and abilities for the purpose of assessment. The tool of such measurement is a test – a system of tasks of a specific form, content, arranged in increasing complexity.

The use of tests is effective for improving the terminological competence in professional vocabulary. The new way of presenting the material allows to study the terms not only by performing traditional training exercises, which are presented in the classroom, but also offers the use of a variety of electronic resources [13, 14, p.99]. The introduction of electronic testing at Ternopil National Medical University as an element of learning new terms helps to supplement the existing standard forms and methods of teaching and to modernize the methods of control of students' knowledge. When preparing and conducting testing on the Moodle platform, the teacher can use its capabilities, through which he/she organizes the verification of the studied material so that the forms of learning correspond to the goals and objectives of specific classes.

Computer tests are perceived positively by students, because the verification of results is automatic, and therefore, the influence of the human factor is excluded. In addition, as it turned out, such tests contribute to better learning of new terms, because in the future students can easily reproduce examples of them. Furthermore, they receive a score immediately upon completion of the test, which also contributes to a better perception of such tests on an emotional level. These elements of the application of the Moodle system for the formation of terminological competence are extremely effective. Students can use as much learning materials as they need to memorize new professional terminology and this greatly facilitates the control of students' learning activities. These elements allow to track the work of each student individually and the quality of its implementation, as well as to encourage students to work more effectively. This significantly saves the teacher's time due to automatic verification.

After doing the tests, the teacher can also analyze the performance of students from the relevant chart (Fig. 6).

The method of organizing the process of knowledge control depends entirely on the teacher – tests can be at the end of each topic, and a presentation can be created only with test tasks, which can be placed at the end of each structural section of the course.

If the test is for self-examination, time limits are not appropriate. If the knowledge of a module or topic is being tested and graded, attempts to take the test at home using an abstract should be prevented. Then the start time and end time of the test are set, after which the teacher must immediately record the grades. There may be a requirement for the student to successfully pass the test before moving on to the next topic. Then you can only set the "Time limit (minutes)" without setting the start and end of the test and thus allowing it to be done from anywhere.

The "Random order of answers" option provides for random mixing of items within the question for each attempt. In the "Attempts" section, the "Allowed" option can limit the number of test attempts.

In the remote Moodle platform for the course there is a general list of test questions ("Question Bank"), which belong to hierarchically ordered categories (button "Questions on the course control panel"). You can combine different tests from the course questions. You can view the test results on the appropriate page. The system collects data on the date and time of the test, the student, the course / lecture where the test task was placed, and the overall grade obtained.

For our study, we analyzed the effectiveness of using the electronic system Moodle for the formation of terminological competence of first-year students (specialty 226 "Pharmacy") at I. Horbachevsky Ternopil National Medical University in 2021-2022 academic year.

90 students studied in the first year of the Faculty of Pharmacy. We divided them into two groups. 45 students studied grammar material and course vocabulary without using the Moodle system. 45 students used the electronic system while studying each topic of the course and assessing the mastery of vocabulary. After completing the discipline, students wrote a final test to verify the mastered Latin medical terms.

As can be seen from the data shown in the diagram (Fig. 7), the success of students who studied the discipline "Latin" using the Moodle system has increased significantly.

CONCLUSIONS

Fluency in medical terminology is a condition for successful professional communication of future specialists. Among the types of professional competence, the analysis of terminological competence deserves special attention, because in-depth general knowledge and professionally oriented speech skills affect the language of the profession, especially its terminological system. Thus, the formation of terminological competence of future medical workers involves mastering special terminology in Latin classes, as a prerequisite for further use of acquired knowledge in other disciplines, as well as literacy in professional terminology. Terminological competence, which students acquire while studying Latin terminology, is the main one in their further professional and scientific activities.

When creating educational and methodological complexes for the formation of terminological competence, the means of teaching, as well as the ways of presenting educational material and the principles of organizing the educational activities of students become important. The electronic platform Moodle, which has a wide range of resources for teaching and testing, is able to expand the communicative competencies and skills of students needed to effectively master professional Latin terminology. The Moodle system has the optimal set of resource opportunities for the implementation of blended learning – classroom and extracurricular, which is its main advantage. The following advantages of the Moodle system include: accessibility and unlimited number of users (creation of a virtual community of students and teachers to implement learning management strategies); creation of conditions for independent work (availability of a real educational process "without leaving home" provided that there is access to the Internet or in a computer class); individualization of learning (reproduction of a student as a person in his/her individual experience, taking into account the characteristics of each student); development of cognitive interests, activation of creative potential of the student (motivates to awaken and keep the interest of the individual in active learning activities), instant feedback between teacher and student. Using the Moodle platform for teaching Latin and medical terminology, teachers can create an environment for lifelong learning with unlimited control, modification, archiving, viewing, etc., and most importantly – for close interaction between students and the teacher.

The possibilities of using the electronic platform Moodle for the formation of terminological competence in the study of Latin described in the article do not cover all the problems concerning the efficiency of mastering by students the professional terminology, and that creates perspective for further scientific research.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Public management of public healthcare under the COVID-19 outbreak: experience of Ukraine

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ABSTRACT

Aim: The research is aimed to study certain aspects and experience of functioning of the Ukrainian Public Healthcare public management mechanisms during an outbreak of the acute respiratory disease COVID19.

Materials and Methods: The studied materials include personal observations and accumulated practical material, as well as generalization of the collected data and their empirical treatment, conducted by the scientists, according to the present legislation requirements. The study was held using general scientific methods, including observation, description of results, specification and statistical data generalization.

Conclusions: Generalization, arrangement and analysis of the Ukrainian experience of the Public Healthcare public management during the outbreak of the acute respiratory disease COVID19, provides exchange of experience between all subjects of the process. This helps to produce certain practical decisions, aimed at effective responding of the state healthcare system onto management of the COVID19 outbreak. Such activities are also directed at detection of flaws in the whole system, with their subsequent correction, and elimination or neutralization of possible negative outcomes.

To adopt the priority activity directions within public relations, which make the subject of the study, the authors have studied a complex of activities against spread of the COVID19 in 2019-2020. These activities include issues, related to prompt responding onto the infection spread and approving quick professional decisions; fulfilling epidemiological supervision and introducing anti-epidemic activities; providing diagnostics, and accessibility of the safe and high-quality vaccine.

KEY WORDS: healthcare, public health, COVID19, anti-epidemic protection, medical-biological emergency

Wiad Lek. 2024;77(1):94-104. doi: 10.36740/WLek202401112 DOI

INTRODUCTION

In 2015, the Government of Ukraine initiated transformation processes within the healthcare system, in order to improve quality of medical service and provide new financing mechanisms.

The advances in the healthcare system, which didn't require enormous personal expenses of the patients, were introduced through modernizing and integrating health service, as well as modifying financial agreements on the health service provision, which will affect the performance and improve quality of the health service. A turning point in this process was approval of the new law on the healthcare financing – the Law of Ukraine "On State Financial Guarantees of Medical Service" [1] in 2017. The law defined a medical package, called the Program of Medical Guarantees (PMG), which combined most state expenses for the healthcare. The National Health Care Service (NHCS) was founded as well, performing the role of the strategical procurement organization for the Program. The main approach is that the Program of Medical Guarantees, expanding with time, will include all kinds of medical service. The system will be financed from numerous sources, from those based on the history data, to evidence results, which will define the patient's medical service according to their needs.

The review of the first healthcare reforms, which were introduced by the WHO and the World Bank, was published in 2019 [2]. The review included the results of reforms since 2016 in five key branches and provided further recommendations. The most challenging were: management, financing (fiscal space, revenue collection, mechanisms of joining the assets), strategical procurement of primary medical and hygienic services, preparation for the strategical procurement of specialized medical care and presenting the guaranteed service package.

After two years of introducing the reform, the healthcare system financing significantly improved, which now calls for necessity of re-estimating the present situation, to define the following steps. A lot of advances, both in the institutional reforms, and the extended approach to the medical service, have been made recently. The number of people in the primary medical care has increased to 31 mln., i.e., over 75% of the Ukrainians have signed declarations with their family doctors, and are now using the package of the primary medical care(PMC). The program "Affordable drugs", introduced by the Government in 2017, was in 2019 included into the Program of Medical Guarantees, being supervised now by the National Service of Healthcare of Ukraine, and 2.8mln of Ukrainians have already received drugs by this Program.

The list of the medical services, included in the Program of Medical Guarantees, is expanded, as nowadays the Program includes the specialized and emergency medical service. Since 2021, the package includes the tuberculosis treatment, mental health services and the COVID19 vaccination services. The process of changing the inpatient treatment charging mechanism, with changes in reporting about the inpatient patients according to the diagnosis groups, within introduction of financing, according to the diagnostic groups, has been initiated. The electronic system of Healthcare (ESHC) is being developed, thus providing e-declarations with the family doctors, issuing e-prescriptions by Program "Affordable drugs" and e-referral, filling in the patients e-charts, etc. The Government has approved of the basic hospitals list, which represents the basis of an effective network, where the investment and innovative processes on perfection of the inpatient services are held.

Due to the COVID 19 pandemics, the levels and mechanisms of the healthcare service have been corrected, which includes new packages of examination, emergency care, inpatient treatment due to COVID 19, and vaccination. The package also includes short-term bonuses for the personnel, working in institutions dealing with the COVID 19 patients. At the same time, due to the COVID 19 pandemics, introduction of some aspects of the healthcare financing has been postponed, e.g., scheduled transformation of the diagnostic group services covering.

The article presents analysis of the main actions of the National Health Service of Ukraine, as a component of the public management system, onto the COVID 19 outbreak, within provision of the public health of population.

AIM

The aim of the study represented in this paper is to research basic aspects and experience of public management of the System of Health Care of Ukraine under the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, outbreak.

The priority directions of the future public relations branch development are based on analysis of measures, taken by responsible public managers in the country, according to the accepted standard acts, which were approved as programs of managing the infectious disease outbreak, as well as the international experience. The study also aims to find the ways of improving the effectiveness of the state institution responding onto the appearing and identified threats, taking measures against the crisis situations in the public health, etc.

MATERIALS AND METHODS

The study is based on the materials, collected by the scientists, which includes their own observations, accumulated factual materials, analysis of the national legislation of Ukraine as well as the international experience. Then, the received data were generalized, followed by empirical analysis, to make appropriate conclusions.

The study is performed by the general scientific and special study methods, including observation, description, systematization, study of the products (results) of activity, generalization and specification of the statistical data, etc. The structural-functional analysis method has been used to define modern trends in fulfillment of the healthcare public management functions, within the public health provision challenge. The generalization and comparison method has been used to compare the present condition of public management of the Healthcare of Ukraine, and to assess opportunities of the international experience adaptation for Ukraine. The synthesis and analysis methods predisposed for providing practical recommendations on perfection of the public management of the healthcare, within provision of the public healthcare service, under the acute respiratory infection COVID19 outbreak.

REVIEW AND DISCUSSION

In 1920, while defining the public health notion, C.E.A. Winslow stated that «Public Health is the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing services for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health» [3].

According to the WHO definition, health is a state of complete physical, mental and social well-being, not just absence of the disease. Health is defined as ability to adapt, and manage one's physical, mental and social problems during one's life. Public health is a subtype of health, representing the health of social communities united by their age, gender, profession, social-economic and other characteristics, as well as total health of all population. The public health consists of the health of separate people.

The health of the population is a greatest value and required condition of the social-economic progress of the country. Providing optimum conditions for personal potential during one's life, reaching the European standards of life quality and population welfare represent main tasks of our country, accepted under the Agreement on Association between Ukraine and European Union, European Community on Atomic Energy and countries- participants [4].

The European program, 2020-2025: Common actions for stronger health define the priority tasks for the years to follow in strengthening the population's health, including the region of Ukraine. In particular, the program defines, that the "countries- members of the WHO, particularly those in Europe, are decisive about fulfilling three interrelated strategic priority tasks, presented in the 13th Common Activity Schedule of the WHO for 2019–2023: aiming at universal coverage of population by the healthcare (Universal Health Coverage, UHC); intensified protection of children against emergencies in the healthcare; and providing healthy life style and promoting welfare to people of all age groups. These main priorities, announced in the AIMS of Permanent Development (APD) till 2030, are connected with three ambitious tasks before the healthcare sector, as the "three billion" aims [5, c. 6].

The Constitution of Ukraine [6] provides the right of every human for the healthcare, medical care and medical insurance.

Conceptual principles of the Public Healthcare in Ukraine are represented in the appropriate Concept, which defines the |system of public health as a complex of instruments, procedures and actions, which are performed by the state and non-state institutions, in order to strengthen people's health, prevent diseases, increase longevity and duration of the working age, and promote healthy life style by joining efforts of the community" [7].

Many Ukrainian scientists dedicated their studies to public healthcare management, like Knyazevych V.M. [8], Rozhkova I.V. [9], Tkachova N.M. [10], Baiieva O.M. [11], Volos B.O. [12], etc. The problems, related to the public management under crisis emergencies, were revealed in papers by Sytnyk G.P. [13], Prykhodko I.I. [14], Belai S.V., Bondarenko O.G.[15], Mykhnenko A.M. [16], Volkov I.M. [17], etc. Foreign experience of advances in the public healthcare management system is represented in papers by Brown T. [18], Kauplan G. [19], Hunter D. [20].

So, it can be concluded, that the theme of this article is quite interesting and important, as for its scientific coverage.

The complex study of the public management mechanism, in whole, reveals its component mechanisms:

- economic – mechanism of management of the bank, monetary, currency, credit, taxation and insurance domains;
- motivation – combination of the team administrative and social-economic factors which encourage highly effective performance of state officers;
- organization - objects, subjects of public management, their aims, tasks, functions, management methods, organization structures, as well as results of their function;
-political – mechanisms of development of the economic, social, financial, industrial policy, etc.
- legal – standards which are the laws, decrees of the Supreme Rada of Ukraine, orders of the President of Ukraine, decrees of the Cabinet of Ministers of Ukraine, and other legislative acts [21].

The outbreak of epidemics in Ukraine necessitated question of development of the laboratory network, renewing the material-technical facilities for increasing opportunities of laboratory studies, introducing automated processes, improving service quality, controlling the quality, etc. In the beginning of the epidemics, on 01.01.2020, the laboratory centers of the Ministry of Health and Center of Public Health were insufficiently supplied with the facilities (an automated station for taking samples for the RNA extraction -1 unit; amplification facilities – 31 units). The virusological reference-laboratory of the Public Health Center contained test-systems for just 3000 Coronovirus samples. Thus, the laboratory centers of the Ministry of Health and Center of Public Health could make only 200 tests a week.

To provide direct organization and coordination of activities aimed at management of the medical-biological emergency on the state level, associated with the COVID 19, the Staff Quarter of Eliminating the Consequences of the Medical-Biological Emergency of the state level, related to COVID 19 spread, was then also founded (herein – Staff Quarter on Eliminating Consequences of the Emergency).

In 2020, 158 Instructions of the Chief Executive of eliminating the medical biological emergency of the state level in Ukraine, associated with COVID 19, were issued, and in 2021 (on the 19.05.2021) – 44 Instructions.

Since first COVID19 case in Ukraine, epidemiological supervision after COVID19 at local/regional/national levels has been introduced, which includes collecting and analysis of the data on the registered cases, monitoring contacts of COVID19 patients, planning and implementing the preventive and anti-epidemic measures.

The diagnosing procedure of the COVID 19, which would correspond to the international recommendations, was approved.

In State Institutions "|Centers of Public Health of the Ministry of Health of Ukraine", the Information- Analytical Group on the Coronavirus Disease COVID 19 was founded (according to the order of the Center, issued on 17.06.2020, reg. № 13-од), which provided data generalized analysis and epidemic situation analysis, regarding peculiarities of the COVID19 spread in various administrative regions.

In May 2020, the Electronic Integrated Infectious Disease Surveillance System (EIIDSS, or EIDSS) started functioning, being the only instrument of such supervision. After 6 months of successful function, access to the EIDSS was granted to district specialists of the public health institutions. In July 2021, the system contained information about more than 3,300,000 cases of COVID 19, more than 780 doctors (of district, regional institutions) were registered in the system, which represented 274 health care institutions.

The EIDSS is quite flexible, as it contains all cells for collecting information about COVID 19 cases, which is urgently transferred to all interested institutions (observing the legislation and medical privacy principles), for making managerial decisions to prevent spread of the COVID19 in Ukraine.

To improve function of the EIDSS, information data exchange between the Electronic System of Health Care (ESHC) was introduced, for digitalization of the Emergency Alarm in case of infectious diseases, Standard 0/58o. Nowadays, such exchange functions for the COVID 19 cases.

At present, the EIDSS is being perfected, to expand opportunities of analysis, visualization and reporting module and improve performance of the reporting module and general database.

From March 2020 till May 2021, thirty-five decrees and orders of the Cabinet of Ministers of Ukraine regarding the quarantine, restricting ante-epidemic measures, and emergency of COVID19 were issued. Also, 58 decrees of the Chief Sanitary Officer of Ukraine, which regulated anti-epidemic actions and recommendations on enactment of various activities, were issued.

This provided effective and free COVID19 diagnostics and testing opportunities for population, thus ensuring its accessibility and affordability to all groups.

Within the Ministry of Health of Ukraine, the COVID19 testing is conducted by the laboratory centers of the Ministry of Health of Ukraine, the State Institution "Center of Public Health of the Ministry of Health of Ukraine", and the State Institution "Ukrainian Research Anti-plague after I.I. Mechnikov, affiliated to the Ministry of Health of Ukraine".

During 2020-2021, technical facility assets and personnel characteristics in these institutions improved significantly. This was reflected in purchase of 58 automated stations for taking samples for the RNA extraction, 55 amplification facilities, 4 robotic and automated systems, which autonomously provide the RNA extraction and introduction of amplification mixture. Additionally, 4615 laboratory staffs of the Ministry of Health of Ukraine were directly engaged in managing the COVID19 cases, receiving additional bonuses for this, which made up to 300% bonus to their salary.

These measures were taken to increase the number of the studies from 200 to 70, 000 tests a day by polymerase chain reaction (PCR) (only in the state healthcare institutions), improve epidemiological investigations procedure, detection of contact people, and introduction of the electronic system of infectious diseases surveillance.

Control over the COVID19 was realized through the Order of the Ministry of Health of Ukraine, issued on 28.03.2020, № 722 "On Organizing Medical Care for Patients with Coronavirus Disease (COVID 19)" [22], which distinctly defines criteria of the PCR laboratory tests procedure, performed to people with suspected COVID19, contact people and risk group employees. The epidemiological surveillance algorithms were introduced to prevent aggravation of the epidemiological situation in the country under the quarantine conditions, as well as in case of quarantine ease. These algorithms are updated and adapted to the current requirements, as the changes in emergency oxygen support have just been introduced.

An appropriate adequate access to the COVID 19 vaccine for the Ukrainian population, as well as control of the related processes, has been provided due to the approved by the Ministry of Health of Ukraine Order, issued on 24.12.2020, № 3018 [23], Route Map on Introduction of Vaccine against COVID 19 and organizing vaccination in response to the pandemic COVID 19 in Ukraine in 2021-2022.

According to the Route Map, a multi-level campaign on vaccination against COVID 19 will last during 2021-1st quarter of 2022, held in 5 stages.

In order to improve management of the vaccination against COVID 19 campaign, by the Decree of the Cabinet of Ministers of Ukraine from 12.04.2021 №340-р,

there was approved "National Plan of Vaccine-prevention of the Acute Respiratory Disease COVID-19, Caused by Coronavirus SARS-CoV-2, till 31 December 2021" [24]. The plan defines a minimum required monthly number of vaccinations, sources and terms of delivery of vaccines for specific prevention of COVID 19, and responsible people for plan fulfillment. The final aim is vaccination coverage of most adult population of Ukraine (23, 939, 194 people) by 31 December 2021, for shaping the collective immunity to COVID-19.

In the beginning of 2020, a legal basis (temporary) for operative introduction of emergency actions on prevention and treatment of the coronavirus disease COVID19 was provided, in particular, possibility of purchase of the necessary goods and services without keeping to the procedures of the Law of Ukraine "On Public Procurement"; 100% deposit for such goods and services; exemption of drugs, medical items and medical facilities, used for prevention and fighting the coronavirus disease COVID 19, from the border tax and value-added tax.

In particular, the Law of Ukraine «On Introducing Changes to some Legislation Acts of Ukraine, Directed at Prevention of the Spread of Coronavirus Disease COVID19 from 17 March 2020 № 530-IX [25], the Law of Ukraine "On Public Procurement" was modified. Also, the Cabinet of Ministers of Ukraine adopted the Decree from 20 March 2020 № 225 «Some Issues of Procurement of Goods and Services, Necessary for the Actions Aimed at Prevention of Spread, Localizing and Managing Outbreaks, Epidemics and Pandemics of the Acute Respiratory Disease COVID 19,Caused by Coronavirus SARS-CoV-2, in Ukraine» [26] and № 224 «On Approving the List of Goods (Including Drugs, Medical Items and/or Medical Facilities), Necessary for the Actions, Aimed at Prevention of Spread, Localizing and Management of Outbreaks, Epidemics and Pandemics of Acute Respiratory Disease COVID 19, Import of which into the Territory of Ukraine and/or any Operations of Supply of which in the Tax Territory of Ukraine are Exempted from the Value-added Tax» [27]. Further, the Decree of the Cabinet of Ministers of Ukraine from 20.03.2020 №225 became invalid, due to the Decree of the Cabinet of Ministers of Ukraine from 22 September 2021 №1012 «Some Issues of Procurement of Medical Items, Necessary for Actions Aimed at Prevention of the Spread, Localization and Management of the Outbreaks, Epidemics and Pandemics of the Acute Respiratory Disease COVID 19, Caused by Coronavirus SARS-CoV-2» [28].

Considering the above mentioned, it became possible to supply the individual protection items to all medical personnel groups.

So, the State Enterprise «Medical procurement of Ukraine» purchased the following individual protection items:

- Medical masks – 6, 647,040 units;
- Protective shields – 29, 567 units;
- Disposable protective clothes (gowns, scrubs)– 2, 089, 426 units;
- Re-usable items (gowns, scrubs)– 1, 006, 095 units;
- Respirators – 1, 233, 810 units;
- Gloves – 4, 793, 880 units.

A thorough preparation for expanding the medical and technical requirements for the procured goods was fulfilled. Thus, the elements which narrowed the participants group and discriminated the participants were eliminated. Owing to the increase of the participants' number, as well as successful negotiations, 1.037 billion hryvnas were saved. The saved money was used to purchase additional individual protection items, which included 20 mln. masks.

Using the financing of the reserve fund of the State Budget of Ukraine in 2020, within the budget financed program, state budget code of expenses and crediting (SBCEC)2301700 "Supplying with the Individual Protection Items during Anti-epidemic actions, Aimed at Management of the Acute Respiratory Disease COVID-19, Caused by Coronavirus SARS-CoV-2, in Ukraine" , biohazard suits were bought - – 71 374 units.

The Ministry of Health of Ukraine provided financing due to the following documents: due to accepted by the Cabinet of Ministers of Ukraine Decrees from 06.05.2020 № 372 "On Financing of Certain Activities, Aimed at Prevention of Spread, Localization and Management of the Outbreaks, Epidemics and Pandemics of the Acute Respiratory Disease COVID19, Caused by Coronavirus SARS-CoV-2", from 09.10.2020 № 922 "On Introducing Changes to the Decrees of the Cabinet of Ministers of Ukraine from 20.10.2020 № 225, and from 06.05.2020 № 372", from 28.10.2020 №1083 "On Financing of Certain Activities, Aimed at Prevention of Spread, Localization and Management of the Outbreaks, Epidemics and Pandemics of the Acute Respiratory Disease COVID19, Caused by Coronavirus SARS-CoV-2", from 02.12.2020 № 1179 "On Introducing Changes to the Paragraph 1 of the Decree of the Cabinet of Ministers of Ukraine from 06.05.2020 № 372", and approval Letters of the Committee of the Supreme Rada of Ukraine on Budgeting, by the budgeting program SBCEC 2301230 "Providing Responding Ability of the Public Health System onto the Outbreaks of the Acute Respiratory Disease COVID19, Caused by Coronavirus SARS-CoV-2, and Providing with the Individual Protection Items Paramedics and the Primary Institutions Hospitalizing Patients with the Acute Respiratory Disease COVID19, Caused by Coronavirus SARS-CoV-2, Budgeted from the Fund Against the Acute Respiratory Disease COVID 19, Caused by Coronavirus SARS-CoV-2", within the expenses for these tasks. This fi-

nancing was due to the following budgeting programs:

SBCEC 2301230 "Providing responding ability of the public healthcare system onto the outbreaks of the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, and supplying with the individual protection items paramedics and personnel of the primary institutions of hospitalizing patients with the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, from the Fund Against the Acute Respiratory Disease COVID 19, Caused by Coronavirus SARS-CoV-2, and its consequences", in particular, 3,979,992.3 hryvnas;

SBCEC 2301240 "Procurement of the artificial ventilation machine financed from the Fund Against the Acute Respiratory Disease COVID 19, Caused by Coronavirus SARS-CoV-2, and its consequences", in particular, 100,000.0 hryvnas;

SBCEC 2301150 "Procurement of the facilities for the admission wards of basic healthcare institutions, financed from the Fund Against the Acute Respiratory Disease COVID 19, Caused by Coronavirus SARS-CoV-2, and its consequences", namely, 2,302,620.0 hryvnas;

SBCEC 2301220 "Advancement of emergency care system", 922,568.9 hryvnas.

On 02.04.2021, the cash expenditures made up, by the SBCEC 2301230 – 3,288, 630.3 hryvnas, including those for procurement of:

- individual protection items for the Healthcare institutions, providing emergency care to patients with the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, for hospitalizing patients with the disease and providing emergency care with the medications, termed using the international non-patented names (INPN) «Remdesivir», «Tocilizumab», and «Immunoglobulins, normal human, forintravascular afm.»; which was aimed to cover needs of the Healthcare institutions in these medications for providing emergency care to the inpatients with the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, in particular – 797,550.4hryvnas;
- express- tests for detecting antigen of coronavirus SARS-CoV-2, aimed to cover the needs of the Healthcare institutions, which perform primary diagnostics of the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, in particular – 988,863.8 hryvnas;
- individual protection items, laboratory facilities and consumable items for the laboratory studies, necessary for the laboratory subdivisions of the Ministry of Health of Ukraine responding at outbreaks of the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, in particular – 985,708.3hryvnas;
- procurement of services for laboratory studies (tests for the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2) by the PCR method, in particular –100,000.0 hryvnas.

The recalled financing of the laboratory subdivisions of the Ministry of Health of Ukraine made up 1,502,216.2hryvnas, which is 93.5 % of the planned budgeting of:

- services of laboratory studies (tests for the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2) by the PCR method, in particular – 38,354.6 hryvnas;
- bonuses to medical and other personnel of the laboratory centers of the Ministry of Health of Ukraine, directly engaged in management of the incidence of the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, in particular – 498,663.7 hryvnas (Decree of the Cabinet of Ministers of Ukraine from 06.05.2020 № 372 "On Financing of Certain Activities, Aimed at Prevention of Spread, Localization and Management of the Outbreaks, Epidemics and Pandemics of the Acute Respiratory Disease COVID19, Caused by Coronavirus SARS-CoV-2");
- bonuses for medical and other personnel of the laboratory centers of the Ministry of Health of Ukraine, directly engaged in management of the incidence of the acute respiratory disease COVID 19, caused by coronavirus SARS-CoV-2, in particular – 478, 153.3hryvnas:
- for SBCEC 2301240 – 84,000.0 hryvnas;
- for SBCEC 2301150 – 2,302,620.0hryvnas;
- for SBCEC 2301220 – 728,068.0hryvnas.

Within the financing, total purchases, distributed according to the orders of the Ministry of Health of Ukraine:

for SBCEC 2301230:

- "Express tests for detecting antigen of coronavirus SARS-CoV-2, to provide needs of the healthcare institutions, which make primary diagnostics of the of the acute respiratory disease COVID19, caused by coronavirus SARS-CoV-2", in particular – 5,919, 800 units;
- «Remdesivir» – 28,200 units;
- «Tocilizumab» – 3,064 units;
- «Immunoglobulins, normal human, forintravascular afm.» – 10,727units;

for SBCEC 2301240 – 200 artificial lung ventilation apparatuses units;

for SBCEC 2301150 – 161 computed tomographs units;

for SBCEC 2301220:

- Specialized sanitation vehicle, type B – 273 units;
- Specialized sanitation vehicle, type C – 143 units.

In order to restore the anti-epidemic protection system, the Law of Ukraine *project* "On System of Public Health" (registr. № 4142 from 22.09.2020). This Law project stipulates for a centralized model of the public

health development, which includes performing the tasks and operative functions by the Ministry of Health-controlled Centers of Disease Control and Prevention in regions. Here, the Center of Public Health of the Ministry of Health is a leading coordinating national institution. The Decree of the Supreme Rada from 04.02.2021 № 1207-IX adopted this Law Project as a basic.

Besides, restoring function of the anti-epidemic protection is realized through re-formatting state institutions – the laboratory centers of the Ministry of Health, into the Centers of Disease Control and Prevention.

After this, changes were introduced into the List of Institutions of Healthcare, approved by the Order of the Ministry of Health of Ukraine from 28 October 2002, № 385, now the changes in Conditions of Pay to the healthcare personnel, approved by the Order of the Ministry of Labour and Ministry of Health from 05.10.2005m № 308/519, are being agreed.

The State Institution "Center of Public Health of the Ministry of Health of Ukraine", by the Order of the Ministry of Health of Ukraine from 09 April 2020 року, № 822, was defined as a National Coordinator in the International Medical and Sanitation Regulations.

The issues, that are being dealt with now, are: preparing the Legal Standard Acts on Risk Communication in the Public Health, approving the List of the Entrance Posts (Control Posts) (EP, CP) through the State Border, and Control Posts of Entrance and Exit (CPEE), which will function in Ukraine in case of the international medical emergency, according to the International Medical Sanitation Regulations. Foundation of the Network of Sanitation Quarantine Subdivisions, in the recalled in the list EP, CP, CPEE, will provide fulfillment of the international obligations of Ukraine, due to the International Medical Sanitation Regulations (2005) (IMSR), as well as providing sanitation security guarding of state border and Ukrainian territory.

Also, the Working Group on design of the Responding Plan onto the Emergencies in the Public Health and Outbreaks of Vaccine-regulated Infections, was created. In June 2021, this document structure was approved, the plan is being elaborated.

The National Contact Center of the Ministry of Health of Ukraine on preventing the spread of COVID 19 has been founded.

On 02 November 2020, the National Contact Center of the Ministry of Health of Ukraine, on preventing the spread of COVID 19 started its function. The contact center telephone number is 0-800-60-20-19, which is a free number for all telephone networks in Ukraine.

One hundred and fifty operators worked in the Contact Center, more than 698 767 calls were answered. Also, there were provided additional services of inquiry for the mobile team visit (with over 8000 mobile team visits performed); and for remote consulting (16 physicians working in the center, with over 14000 consultations provided).

Activities on regulation of the disinfection medications and their trials were taken.

The COVID 19 epidemics showed importance of production and access of people to high-quality, effective and safe disinfection medications.

There was approved the Order of the Ministry of Health from 03.09.2020 № 2024, "Methods of Studies of Specific Action, Safety, and Quality of the Disinfection Medications and their Practical Trials".

Activities on regulation of state supervision (control) in sanitation legislation were taken as well.

In order to provide the effective functioning of the State Consumer Protection Service, fulfilling the tasks of schedules/emergent supervision and control activities over fulfilling legal standards of sanitary and epidemic population welfare, the Order of the Ministry of Health of Ukraine from 04.08.2020, № 1788, was enacted: "On Approving the Unified Sample of Act of Results of the Scheduled/emergent Supervision and Control Activities over Fulfilling Legal Standards of Sanitary and Epidemic Population Welfare", registered in the Ministry of Justice of Ukraine on 16 December 2020, № 1244/35527.

The issue of blood safety was also regarded by the introduced and accepted by the Supreme Rada of Ukraine Law of Ukraine "On Safety and Quality of the Donor Blood and Blood Components" from 30.09.2020, № 931-IX.

The Ministry of Health of Ukraine prepared, and the Cabinet of Ministers of Ukraine approved (09.10.2020, Decree № 965) experimental Project on preparation of specific (hyperimmune) blood plasma with antibodies against SARS-CoV-2, for contract manufacturing of immunoglobulin, used for treatment of COVID-19.

Within the State Institution "|Center of Public Health of the Ministry of Health of Ukraine" the transfusion center was founded, to coordinate and monitor performance of the institutions and blood centers, as well as manage the blood supply system function in the state.

According to information data treatment, regarding national conditions of problem solution, basic directions and suggestions of increasing effectiveness of the public health public management mechanisms under the COVID 19 were put forward:

- Still urgent remains the necessity of adopting basic law about the public health system, as well as necessity of its enactment legal standards;
- The network of the analytical resources, joining the research institutions and the Ministry of Health Laboratory Centers, is to be updated;

- Instruments of management of biological risks should be introduced in practice;
- Legislation regarding protection of people against infectious diseases, sanitary and epidemiological welfare of people, and the Public Health System needs an update;
- Financial, technical, and personnel resources of Public Health need improvement;
- Of urgent necessity is to provide permanent financing of the program "Public Health and Anti-epidemic Activities", and to ensure its enactment;

The regulations on sanitary protection of territory of Ukraine require changes;

- The Algorithm of responding onto the emergencies, according to the International Medical and Sanitary Rules, should be adopted;
- One should provide extended accessibility and affordability of the safe and high quality vaccine against COVID 19 for the population;
- In order to shape the collective immunity against COVID 19, it's necessary to cover with vaccination majority of adult Ukrainians, as quickly as possible, best – by 31.12.2021;
- National schedule should be realized, the number of the unused vaccines for the specific prevention of the acute respiratory disease COVID 19 should be reported;

The National Schedule of vaccine prevention of COVID 19 by 31 December 2021 requires periodic update, considering real speed of the vaccination campaign;

- The legal standard acts, regulating immune-prevention, need complex re-considering and adjustment with the international standards;
- Target groups of people, who did not receive all boosters, must be covered with the campaign;
- Educational curricula on immune-prevention in schools and universities should be re-considered and adjusted;
- General information-educational campaigns on actual issues within the immune-prevention need further promotion;
- It's crucial to provide effective procurement and supplies, within common with the World Bank projects;
- The priority directions of technical support from the UN, aimed at management of the COVID, and their financing, should be defined;
- The effective communication with people through the National Contact Centers of the Ministry of Health of Ukraine program should be expanded;
- Studies of improvement of the anti-epidemic activities should be held;
- In order to provide the necessary conditions for functioning of the affiliated to the State Institution "Center of Public Health of the Ministry of Health of Ukraine" reference-laboratories function, the laboratories should be reconstructed;
- The Legal-Standard Acts which regulate collection, treatment and reporting data on the emergency, related to the COVID19 spread, should be revised and updated, to decrease the load of enquired information, which is no longer relevant, and avoid doubling the data stored in old documents;
- The operative data provided to the head of the Group on elimination of consequences of the medical-biological natural emergency in the state, related to the spread of coronavirus disease COVID19, should be verified;
- The function of the Electronic integrated Information System of Surveillance over the Infectious Diseases should be maintained during the following periods;
- The Legal-Standard Acts on organizing medical care to the patients with the coronavirus disease (COVID-19) should be updated, considering the existing world data on the peculiarities of COVID 19 development, especially regarding the new virus strains;
- In the short-term prospective, people over 60 years are prioritized in vaccine coverage;
- It's necessary to improve the functions,duties and algorithms of actions of the primary and secondary outpatient care providers, within the management of the COVID 19, in particular, epidemiological investigation of infectious disease cases;
- The Algorithm of epidemiological investigation of epidemics and infectious disease outbreaks should be approved;
- Emergent actions of employing or re-distributing the personnel - medical specialists of appropriate institutions, should be taken, to provide sanitary and epidemiological welfare of people;
- One should take measures to avoid future situations with absent individual protection items supplies, both for the medical care provides, and people of Ukraine;
- State protection of the immune-biological field of Ukraine, production of medical items, should be enacted;

CONCLUSIONS

The issue of optimizing and improving effectiveness of the Public Health public management is related to defining and transformation of the methods and ways of such activity, particularly, in case of emergencies, which is, undoubtedly, an outbreak of the acute respiratory disease COVID19, caused by coronavirus SARS-CoV-2. The management subject in this sphere is the state, represented with its legal representatives

and those people, who compose an ordered, hierarchic system, provided with definitely defined rights and duties, aimed at regulating the object of management. The object of public management is represented with people, institutions, enterprises, mass media, state institutions, local authorities, etc. The means of the state function fulfillment in the sphere, is the organizational and legal mechanisms of the public healthcare public management.

The elaboration of the priority directions within public relations, which makes a subject of our study, should be preceded by the study of actions complex, which are being taken, and may be fulfilled, or are aimed at responding towards the COVID 19. The significant issues of such activity are organizing quick responding onto the infection spread, making professional decisions; providing epidemiological supervision and introducing the anti-epidemic activities;

providing diagnosis, testing and access of the people to a safe, high quality vaccine; providing the individual protection items to medical personnel; solving the issues of financing of medical items, facilities; managing issues related to restoring the anti-epidemic protection of people and restoring function of the national contact-centers; providing state supervision in sanitation legislation. Only according to the common actions of the state and society, confirmed by the firm position of each person, organizing a definite structure of responsible subjects, providing appropriate explanatory and preventive activities, scheduled planning of activities and their appropriate financing, it will be possible to overcome the pandemics, caused by an outbreak of the acute respiratory disease COVID 19.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

The associations of cytokines and gens polymorphisms of β-adrenoceptors in patients with heart failure and some thyroid pathology (literature review and own observations)

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ABSTRACT

Aim: To analyze the role of cytokines in the progression of heart failure (HF) in patients with concomitant pathology of the thyroid gland.

Materials and Methods: The systematization of literature data on the role of cytokines in the progression of HF in patients with concomitant thyroid pathology (TP) was carried out. The results of our own research were presented.

Conclusions: The final chapter in the history of the role of cytokines in the progression of HF has not yet been written. Further studies, including genetic ones, are necessary. The patients with HF have higher levels of TNFβ and IL-6, and a lower concentration of IL-4, compared to the control group. Patients with a fatal outcome of the disease, in contrast to those who survived for two years, have an increased level of TNFβ. In patients with concomitant TP, who had repeated hospitalization, a lower level was registered, compared to that under conditions of a more favorable course of heart failure. Concentrations of cytokines in the blood of patients with HF are associated with gene polymorphisms of the β-adrenoreceptor system: the C-allele of the Gly389A polymorphism of the β1-adrenoceptor gene leads to a decrease in the risk of increasing TNFα; IL-1α increases in the presence of the A-allele of the Ser49Gly polymorphism of this gene. In patients with HF and concomitant thyroid pathology, the risk of IL-6 growth increases in homozygous (C) patients for the Ser275 polymorphism of the β3 subunit of the G-protein.

KEY WORDS: cytokines, polymorphism, thyroid gland, heart failure, genes, β-adrenoceptors

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INTRODUCTION

Cytokines (CN) and other inflammatory mediators may be associated with the development and progression of heart failure (HF) [1]. However, this path of pathogenesis remains insufficiently studied. The dynamics and influence of cytokines on the course of heart failure in patients with concomitant thyroid pathology also remain unclear.

AIM

The aim of this article is analyze of the role of cytokines in the progression of heart failure in patients with concomitant pathology of the thyroid gland.

MATERIALS AND METHODS

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of dynamics and influence of cytokines (CN) on the course of heart failure (HF) in patients with concomitant thyroid pathology (TP). Also, the results of our own research were presented.

REVIEW AND DISCUSSION

The CN, synthesized mainly by leukocytes. This is where their other name comes from, such as interleukins (IL). They are also produced by mononuclear phagocytes and other cells of both the immune and other systems. It is a class of small peptides (8-30 kDa) that regulate intercellular and intersystemic interactions in the body, including stimulation or inhibition of cell growth, differentiation, functional activity and apoptosis, and also ensure the coordination of the action of the immune, endocrine and nervous systems under normal conditions and under diseases [1]. Interleukins are active in low concentrations. Their biological effect on cells is realized through interaction with specific receptors located on the cell membrane. The synthesis and secretion of interleukins is short-

term and strictly regulated. The spectra of biological activity of interleukins largely overlap: one process can be activated in a cell by more than one cytokine. In many cases, synergism is observed in the actions of interleukins. Interleukin and antigen are non-specific factors, so specific diagnosis of infectious, autoimmune and allergic diseases using cytokine level determination is impossible. But determining their concentration in the blood provides information about the functional activity of various types of immunocompetent cells, about the severity of the inflammatory process, its transition to the systemic level, and the prognosis of the disease [1].

Several studies have demonstrated increased expression and release of pro-inflammatory cytokines such as TNFα , IL-1, IL-6, IL-18, cardiotrophin-1 and Fas ligand, as well as several chemokines in patients with HF [2]. The levels of pro-inflammatory CN and chemokines in the plasma are most often increased, directly proportional to the worsening of HF according to NYHA and the decrease of the left ventricular eject fraction (LVEF). Increased expression of inflammatory mediators has been proven in the zone of acute myocardial necrosis (for example, adhesion molecules, TNF, IL-6-related other cytokines and chemokines) [3]. Some of these mediators provide predictive value that surpasses traditional risk markers in accuracy.

The pathogenetic role of pro-inflammatory CNS in HF was confirmed during research on various models of transgenic mice. Systemic administration of TNF to experimental animals in concentrations corresponding to those in the plasma of patients with HF, induces dilated cardiomyopathy [4-6]. Studies in genetically modified mice have also shown a link between the development of HF and IL-6, its receptor subunit glycoprotein (gp) 130, which is common to several CN in the IL-6 family, as well as various chemokines (eg, MCP- 1) and CXCL13 [4]. Proinflammatory CNS can modulate myocardial functions involving various mechanisms. Among them is stimulation of the development of hypertrophy and fibrosis by direct action on cardiomyocytes and fibroblasts, violation of the contractile ability of the myocardium due to a direct effect on intracellular Ca2+ transport and signal transmission through β-adrenoreceptors (β-AR), induction of apoptosis and activation of a number of genes in cardiomyocytes responsible for heart remodeling [5]. Inflammatory mediators may also have an indirect effect on the progression of HF by impairing bone marrow function with the development of secondary anemia; cause inadequate activation of endothelial cells and impairment of peripheral muscle function with induction of systemic inflammation .

During the acute phase of myocardial infarction (MI), CN production is, in fact, a response to damage. Triggers for the release of CN (such as TNFα , IL-6 and IL-1 α in MI, there is ischemia, reactive oxygen species formed in excess during ischemia-reperfusion cause membrane damage, and also stimulate the synthesis of molecular patterns associated with danger, which include ATP, uric acid, mitochondrial DNA, and heat shock proteins. This inflammatory process is a prerequisite for wound healing, scarring and the development of compensatory hypertrophy. Studies have also shown that these proinflammatory CN initiate a cardioprotective signaling cascade known as the "survival pathway" [6]. However, although a moderate cytokine response may be protective, an inappropriate and persistent inflammatory response may lead to the formation of a «maladaptive» situation. In addition, experiments with the participation of animals have demonstrated that with a large MI, the expression of CN genes can remain significantly elevated for a long time, especially in the non-infarcted zone. Levels of late activation of the CN correlate with LV SCD, which was demonstrated 20 weeks after MI in rats .

It remains an open question whether inflammatory processes can be involved in the pathogenesis of HF with preserved PV. Although increased inflammation is a well-known feature of HF with low LVEF, this process has not been sufficiently studied in diastolic HF. However, there are data showing that patients with diabetes and hypertension with signs of diastolic dysfunction, like patients with reduced PV, often have elevated TNF levelsα, IL-1β and IL-6 in the blood [7]. An important role has been proven T-cells in the remodeling of the myocardium, including an increase in the activity of the enzyme lysyl oxidase, which, due to changes in the properties of collagen, affects the increase in stiffness of the myocardium [8]. In mouse models of hypertension and metabolic syndrome, induction of a type I T-helper inflammatory phenotype (i.e., increased levels of TNFα , interferon-γ and IL-18) and an increased level of TFR, which potentially contributes to the development of myocardial fibrosis. In addition, it is known that the infusion of IL-6 in rats leads to concentric LV hypertrophy, an increase in the volume fraction of collagen, and an increase in myocardial stiffness [9]. It was shown that IL-18 increases the expression and production of osteopontin, which stimulates the formation of interstitial fibrosis , and TGF, which increases collagen synthesis and inhibits matrix degradation by reducing

MMP activity [10]. Increased production and decreased degradation of collagen and increased activation of lysyl oxidase-1, which determines the formation of insoluble collagen, can, in turn, eventually lead to LV diastolic dysfunction. These interactions may play a role in adverse myocardial remodeling in patients with HF and reduced LVEF. The results of studies concerning the levels of CNS in HF with preserved PV indicate a complex dysregulation of the cytokine network rather than a simple imbalance between the production of cytokines by T-helper types I and II. This may include increased production of mediators involved in both inflammation and fibrogenesis. Among them are galectin-3, increased activation of T-helpers, which implies hyperproduction of IL-6 and the development of myocardial fibrosis, and at the same time the lack of general regulation of the immune response due to a violation of the function of regulatory T-cells [11].

IL-4 is produced by immune cells, including CD4 + T-helper (Th) lymphocytes and mast cells. Among the many biological effects, the following should be highlighted: IL-4 in pathological processes contributes to the development of lung fibrosis [12], skin, and liver. Studies have shown a positive correlation between systemic IL-4 levels and fibrotic cardiac remodeling in both patients , as well as in animals in the experiment [13]. In addition, previous studies have established that mice of the Balb/c genetic line, which are characterized by a high level of circulating IL-4, have an increased deposition of collagen in the heart, an increase in the size of the LV and a decrease in AF (fibrous cardiomyopathy). Administration of IL-4 neutralizing antibodies significantly reduces cardiac fibrotic remodeling in C57BL/6 mice with coarctation of the aorta [14]. Vascular endotheliocytes express - IL-4 receptors. In the lungs, IL-4 activates endotheliocytes, inducing the production of endothelin-1, which leads to the development of pulmonary hypertension .

Myocardial fibrosis can lead to systolic dysfunction by several mechanisms, including disruption of force generation by myocytes, normal coordination of electromagnetic coupling, and asynchronous myocardial contraction. It was noted that after blocking IL-4 receptors, the development of fibrosis is slowed down and the contractility of the myocardium improves [14].

In the work of N. Peng et al. (2015) demonstrated that IL-4 is associated with an increase in the number of mast cells in the heart [15]. In pathological conditions, these cells can be activated by cytokines, in particular IL-4, which leads to increased secretion of a number of mediators responsible for the development of fibrosis [14]. Peng N. et al. (2015) also found a positive relationship between the functioning of mast cells and the formation of myocardial fibrosis [15].

Scientists from Poland demonstrated that human thyrocytes can themselves synthesize cytokines that activate T and B lymphocytes. The authors demonstrated that in patients with non-toxic goiter there is an increase in the concentration of IL-6 and IL-8 and other CN.

The only specific sign of autoimmune thyroiditis (AIT) is currently considered to be a certain set of morphological changes in the thyroid gland (TG). This gave reason to single out this disease as a separate nosology [16]. The pathogenesis of AIT is based on an autoimmune process, and it leads to partial or complete destruction of the thyroid gland with the development of characteristic morphological changes and secretory insufficiency.

Experimental AIT can be induced in mice by injection of murine Tr (mTg). The disease is characterized by lymphoid infiltration of the thyroid gland, increased production of mTg-specific antigens, and follicular destruction. Although the mechanisms by which CD4 + T cells cause the destruction of the thyroid gland in AIT are not fully understood, it is assumed that under these conditions the production of CNS by T-helper type I plays an important role. The combination of INF-γ and TNF-α produced by the thyroid gland, as well as an increase in the synthesis of INF-γ by lymphocytes, can contribute to the apoptosis of thyroid follicular cells due to the activation of caspases. The activity of AIT may increase after the introduction of IL-12. It is also known that the use of IL-4 can prevent the development of these manifestations [17].

There is an assumption that CNs play a certain role in the genesis of the syndrome of low triiodothyronine (SLT3). In particular, it is known that INF-α and IL-6 increase the risk of developing SLT3 in patients with acute MI and heart surgery [18]. Proinflammatory CN are often increased in SLT3 and are inversely correlated with the levels of thyroid hormones (TH) [19]. In addition, the CN are probably involved in the inhibition of the hypothalamic-pituitary axis, which is often observed in SLT3. This may be the second, after the action of local deiodinases (DY), explanation of the decrease in TRH mRNA production of the hypothalamus during SLT3. The relationship between pro-inflammatory CN and levels of TH was demonstrated in patients with obstructive pulmonary disease and diabetes [19].

Gullestad L. et al suggested that although "too many" of these mediators are maladaptive, "too few" of them may be harmful, illustrating the challenges

of immunomodulatory therapy in HF [20]. Given the central role of the FNPα in the pathogenesis of HF, therapeutic modulation targeting this interleukin has received particular attention. Taking into account the results of a number of studies, it was assumed that the inhibition of TNFα recombinant chimeric sTNFR2 (etanercept) may have a positive clinical effect in patients with HF . However, the Etanercept Worldwide (RENEWAL) randomized clinical trial was subsequently conducted to evaluate the effect of etanercept on morbidity and mortality in patients with HF. Based on the data analysis of 1,500 patients with HF symptoms and left ventricular ejection fraction (LVEF) ≥ 30%, it was established that there was no effect of the drug on mortality, hospitalization, or functional class dynamics [21]. The results of a sub-analysis of the study suggested a dose-outcome relationship, as there was a reduction in hospitalizations/deaths among patients receiving the lowest dose compared to those receiving the highest dose. Another series of studies focused on TNF was the ATTACH trial with a chimeric anti-TNF monoclonal antibody (infliximab) in 150 patients with HF, which was a placebo-controlled phase II trial in HF and LVEF 35%. This clinical trial was stopped at an early stage, because higher rates of mortality and hospitalization were registered in the active group with the use of high doses of the drug [22]. A possible explanation for this unfavorable result is that infliximab binds directly to the transmembrane form of TNF receptors, which ultimately leads to the induction of apoptosis of cardiomyocytes that present these receptors . Although such mechanisms may be useful in some diseases, such as inflammatory bowel diseases, however, they lead to the development of harmful effects in HF. On the other hand, it remains to be determined whether anti-TNF therapy can have a positive effect on HF with preserved LVEF, which is characterized by myocardial hypertrophy and fibrosis.

The failure of anti-TNF therapy has increased interest in a systemic approach to conducting immunomodulatory therapy in order not only to block the harmful effects of inflammatory cytokines, but also to increase the synthesis of anti-inflammatory CNS to restore the appropriate balance during the development of the inflammatory process. In a double-blind, placebo-controlled study, it was demonstrated that intravenous immunoglobulin (IVIg) increased LVEF by 5 units, while no significant changes were observed in the placebo group [23].

Neither immunosorption nor immunosorption was proven to have a positive effect in patients with HF, nor thalidomide [20], but not re-injection of autologous blood [24].

There is more and more evidence of the connection between two regulatory systems - the autonomic nervous system and the immune system [25]. Various studies have shown the presence of sympathetic innervation of lymphatic vessels, nodes and parenchyma of lymphoid organs [26]. At the same time, the immune response can alter the local and systemic adrenergic response. For example, intracerebroventricular administration of IL-1, IL-6, and TNF leads to activation of the central part of the sympathetic nervous system and an increase in norepinephrine metabolism. Peripheral introduction of INF-α or IL-1 causes a long-term increase in sympathetic tone at the level of spleen tissues. The role of such a feedback loop can be regulatory, affecting the specific form of the immune response. All subclasses of T-lymphocytes, with the exception of T-helper type 2, have β2-AR. Stimulation (β2-AR) plays an important role in the proliferation of CD4 + cells. Although the data are conflicting, most studies conclude that stimulation β2 -AR inhibits the proliferation of CD4 + T-lymphocytes [27]. This effect can be observed under conditions of increased levels of cAMP and protein kinase-A (PC-A) in T-lymphocytes [27]. This allows us to make an assumption that the inhibition of the proliferation of T cells β2-AR occurs through the cAMP / PK-A system. Stimulation β2-AR of mature cells in the process of activation leads to suppression of cellular immunity [27].

There is little research on the role β2-AR in the regulation of differentiation and function of B-lymphocytes [28]. Most of the research was done on mice. It was established that stimulation 2 -AR, among other factors, is accompanied by an increase in the formation of IgG 1 and IgM. At the same time, with a decrease in the concentration of HA in the blood plasma of immunodeficient mice and the simultaneous administration of immunized T-helper type 2 and B lymphocytes. It has been shown that insufficient stimulation β2 -AR leads to a significant decrease in the formation of IgG.

IL-4, produced by activated T-helper type 2, binds to its receptors (IL-4R) on the surface of B-lymphocytes to further regulate the formation of antibodies. Stimulation β2-AR of B-lymphocytes modulates this process by using several mechanisms. β2 - AR on activated B-lymphocytes through the cAMP / PC-A system increases the level of IgG 1 protein. In addition, stimulation β2-AR leads to increased expression of CD86 [29]. Activation β2 -AR is also accompanied by a decrease in the production of IL-12, changing the conditions favorable for the differentiation of type 1 T-lymphocytes. It is known that stimulation β2-

AR modulates the immune response, reducing the activity of cellular immunity regulation processes with the strengthening of the regulatory influence of the humoral link of immunity.

A connection between the decrease in density was established β2-adrenoceptors on B-lymphocytes and the presence of chronic rheumatic diseases . Stimulation β2-adrenergic receptors of neutrophils affects the chemotaxis of these cells, apoptosis and the release of a mediator [30]. In vitro studies have shown that stimulation β2 - adrenoceptors of monocytes reduces the formation of pro-inflammatory cytokines IL-1, TNFα, IL-6 and IL-8 by these cells [31]. With a 24-hour infusion of adrenaline 30 ng / kg / min, a decrease in the formation of TNF by monocytes is observed and increased synthesis of IL-10. The obtained data indicate an important role β2-AR in the modulation of the immune response.

Although there have been several studies in animal models demonstrating the anti-inflammatory effects of ACE inhibitors and β-adrenergic blockers, the effect of these immunomodulatory drugs in heart failure in humans appears to be quite modest. Despite the fact that high doses of enalapril significantly reduced the biological activity of IL-6 in heart failure with preserved left ventricular ejection fraction, this drug did not affect other pro-inflammatory cytokines. The influence of β-blockers on the development of inflammation in heart failure in humans is ambiguous and uncertain [32].

The study of the level of cytokines in patients with heart failure and comorbid thyroid pathology remains relevant. Associations of serum cytokine concentrations with gene polymorphisms of the β-adrenoceptor system are also insufficiently studied.

A series of experimental studies demonstrated that the biological effects of interleukins can explain some aspects of the pathogenesis of heart failure. The role of proinflammatory cytokines in HF has been confirmed by various models of transgenic mice. It is noteworthy that systemic administration of TNFα in concentrations comparable to those in the plasma of patients with HF provokes the development of dilated cardiomyopathy in animals [8]. Later studies in genetically modified mice also showed a relationship between IL-6 and its receptor subunit glycoprotein (gp) 130, which is common to several cytokines in the IL-6 family, as well as to various chemokines (eg, MCP-1) and CXCL13) and the development of HF [9]. Proinflammatory interleukins can modulate myocardial function through various mechanisms, including stimulation of hypertrophy and fibrosis by direct action on cardiomyocytes and fibroblasts, impairment of myocardial contractility by direct action on intracellular calcium transport, and signaling through β-AR, induction of apoptosis and stimulation of a number of genes in cardiomyocytes responsible for heart remodeling. Inflammatory mediators may also make a more indirect contribution to the progression of HF through bone marrow dysfunction with the development of secondary anemia, inadequate activation of endothelial cells, and peripheral muscle dysfunction with the secondary induction of systemic inflammation and reflex abnormalities inherent in heart failure [33].

In our study, it was established that patients with HF, compared to the control group, had higher levels of TNFα (by 38.8%, $p < 0.0001$), IL-6 (by 116.4%, $p < 0.0001$) and a lower concentration of IL-4 (by 27.3%, $p < 0.0001$), as well as a higher IL-1 ratioβ /IL-4 (by 37.9%, $p < 0.0001$) [34].

The function of TNF belongs to cellular signaling proteins (cytokines, phosphoproteins), participates in the processes of systemic inflammation, and is one of the cytokines that form the acute phase reaction. TNF is mainly produced by activated macrophages, to a lesser extent it is synthesized by other types of cells (T-helpers, NK-cells, neutrophils, mast cells, eosinophils). The main role of TNF is to regulate the interaction of immune cells, it triggers the process of apoptosis, causes cachexia, inflammation and inhibition of tumor growth, virus replication, regulates the production of pro-inflammatory IL1 and IL6 [35].

IL-1 (English Interleukin-1, IL-1) is a cytokine, a mediator of inflammation and immunity, synthesized by many cells of the body, primarily by activated macrophages, keratinocytes, B-lymphocytes and fibroblasts. Controls the activity of leukocytes, increases the number of bone marrow cells [1]. The existence of two similar interleukin-1s was also discovered:α and β [1].

IL-4 is synthesized by activated T-helper type 2 (Th2), mast cells and eosinophils. It regulates the growth and differentiation of B-lymphocytes, as well as the processes of biosynthesis and secretion of antibodies [36]. This IL affects the production and secretion of IgE and IgG 1 by B-lymphocytes, the switching of Th2 C-genes, the accumulation of eosinophils, the expression of low-affinity receptors for IgE CD23 on B-lymphocytes and mast cells. The cytokine prevents Th1 differentiation and their production of other ILs. IL-4 inhibits the proinflammatory activity of macrophages and their secretion of IL-1, FPN, and IL-6, i.e., ultimately has an anti-inflammatory effect [36].

IL-6 (eng. Interleukin-6, IL-6) – produced by activated macrophages and T-lymphocytes. Can act as

a pro-inflammatory and anti-inflammatory cytokine, stimulates the immune response [36].

According to the results of our study, it was established that patients with HF in combination with low triiodothyronine syndrome and thyroid pathology (TP) (diffuse goiter and autoimmune thyroiditis) probably have lower levels of IL-1β (by 21.9%, p = 0.03) and IL-4 (by 11.5%, p = 0.04), compared to patients without peripheral dysthyroidism syndrome. Patients without TP who died within two years of follow-up had higher levels of TNFα (by 29.2%, p = 0.01), and patients with the achievement of the combined end point (CC) (re-hospitalization due to heart failure decompensation and death) had a tendency to increase the content of IL-1β (by 16.6%, p = 0.05). In patients with HF and TP who had re-hospitalization (PG), the level of IL-4 was significantly lower (by 14.4%, p = 0.04), compared to patients with a favorable course of HF. A similar pattern was found in patients who had CCT (by 14.4%, p = 0.02) [34].

In the works of foreign authors, an increase in the expression and release of pro-inflammatory ILs, such as TNF, has been demonstrated α , IL-1, IL-6, IL-18, cardiotrophin-1 and Fas ligand, as well as several chemokines in patients with HF [9]. Concentrations of pro-inflammatory cytokines in plasma, most often elevated, are directly proportional to the worsening of PK according to NYHA and LVEF [9]. Moreover, some of these mediators have been found to provide prognostic information superior in accuracy to traditional risk markers .

During acute infections, hypoxia or tissue damage, monocytes are the main producers of IL and TNF, which, in turn, activate other links of the immune system . On the other hand, the increased activity of the sympatho-adrenal system, caused by the same factors, is an important regulatory mechanism that optimizes inflammatory reactions . Norepinephrine has been shown to have effects on innate immunity in vivo, including acting as a chemotactic agent for monocytes, as well as affecting TNF-α production . Prolonged or inappropriate stimulation of the sympathetic nervous system can lead to excessive inflammation or uncontrolled infection, leading to pathological effects including toxic shock and tissue damage [37].

The presence of expression of β-adrenoceptors in the ex vivo preparation of human mononuclear leukocytes has been proven [38]. It was demonstrated the expression of β1- and β2-AR subtypes on human monocytes, which caused an increase in the production of IL-1β upon simultaneous stimulation with catecholamines. Using selective antagonists β1 -AR, a pro-inflammatory response of monocytes was proved, which was functionally correlated with the generation of cAMP [38].

On number and activity β -AR and G-protein subunits are affected by the types of polymorphisms in the genes encoding them. This, in turn, can act at the level of interleukins produced by immunocompetent cells.

During the study, we established that in patients with HF, the C-allele of the Gly389A gene polymorphism β1-AR is associated with a decrease in the risk of increasing the serum level of TNF-α > 1.96 pg/ml (OR = 0.48 (0.25-0.93), p = 0.028 – dominant model of heredity; OR = 0.62 (0.39-0.99), p = 0.046 – log-additive model of heredity). In patients with HF with the A-allele of the Ser49Gly gene polymorphism β 1 -adrenoceptors, the level of IL-1 increases β > 2.13 pg/ml (OR 1.82 (1.01-3.27), p = 0.042 – dominant model of heredity). Heterozygous (according to A/G – Ser49Gly gene polymorphism β1-AR) patients with HF have a reduced risk of increasing the level of IL-6 > 2.13 pg/ml (OR 0.44 (0.21-0.93), p = 0.035 – overdominant model of heredity) [39].

We know that β-ARs are located on the membranes of both the endotheliocytes of thyroid vessels and on the cells of the parenchyma of the gland. There are data that the activity of deiodinases (both peripheral and thyroid) may also depend on polymorphisms β-AR. In turn, it should be noted that thyrocytes can produce IL locally. In the genesis of the development of TP, both genetic and inflammatory factors play a role.

We found that patients with HF and TP who have the heterozygous genotype of the Ser49Gly polymorphism (c,145A>G) of the β 1 -AR gene have an increased risk of increasing the level of TNF-α (OR = 4.55 (1.27-16.34), p = 0.028). The risk of increased IL-6 level increases in homozygous (C / C) patients for the Ser275 polymorphism of the gene of GNβ3 in the presence of TP (OR = 5.86 (1.81-19.0), p = 0.003) [39].

In vitro studies have shown that homozygotes for Ser49 (AA genotype) have a lower functional activity of adenylate cyclase compared to carriers of the G allele, but are more sensitive to adrenaline stimulation [40]. Another study found no differences in basal adenylate cyclase activity, but confirmed high sensitivity to long-term agonist exposure. It is possible to assume that the G allele does β1 -AR is less sensitive to adrenal stimulation [40].

We found that the risk of increasing the level of IL-6 increases in homozygous (C / C) patients for the Ser275 polymorphism of the gene of GNβ3 in the presence of TP (OR = 5.86 (1.81-19.0), p = 0.003) [37].

CONCLUSIONS

In conclusion, it should be noted that the final chapter in the history of the importance of cytokines in the formation and progression of heart failure, especially in patients with concomitant pathology, has not yet been written. Further studies, including genetic ones, are needed.

In our studies, it was established that patients with heart failure have higher levels of TNFα (by 38.8%) and IL-6 (by 116.4%), a lower concentration of IL-4 (by 27.3%) compared to the control group. Patients with a fatal outcome, unlike those who survived for two years, had an increased level of TNFα (by 29.2%). A lower IL-4 level (by 14.4%) was registered in patients with concomitant thyroid pathology who were re-hospitalized, compared to those with a more favorable course of heart failure. Concentrations of cytokines in the blood of patients with heart failure are associated with gene polymorphisms of the β-adrenoreceptor system: the C-allele of the Gly389A polymorphism of the β 1 -adrenoceptor gene leads to a decrease in the risk of TNFα elevation (OR = 0.48, dominant model); IL-1α increases in the presence of the A-allele of the Ser49Gly polymorphism of this gene (OR = 1.82, dominant model). In patients with heart failure and concomitant thyroid pathology, the risk of increasing IL-6 increases in homozygous (C) patients for the Ser275 polymorphism of the β 3 subunit of the G-protein (OR = 5.86).

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

COVID-19 associated anosmia in pediatric patients: subject publications review

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ABSTRACT

Aim: To review the publications subject to the problem of COVID-19 associated anosmia incidence in pediatric patients as well as its pathogenesis, diagnostics, treatment and recovery. The peculiarity of pediatric COVID-19 anosmia is due to children accounting for very low percentage of COVID-19 patients (comparing to one in adults), mostly with milder course of the disease. Awareness of anosmia and its proper diagnostics is crucial in children and adolescents, considering it can be the only manifestation in COVID-19 positive pediatric patients.

Materials and Methods: In order to achieve this goal a meta-analysis of information from databases followed by statistical processing and generalisation of the obtained data was carried out.

Conclusions: Publications on COVID-19 anosmia in children and adolescents are less numerous than those concerning adult patients, so it is important to use every single trustworthy one. Anosmia/ageusia may be the only symptom, early identifier and the strongest predictor of COVID-19 infection in pediatric patients. Prospects for further scientific researches. Further researches regarding differential diagnostics of COVID-19 and other infections, including seasonal influenza, manifesting with both olfactory and taste dysfunction as well as anosmia diagnostics in children and adolescents with autistic spectrum and different types of mental disorders are possible.

KEY WORDS: COVID-19 infection, olfaction, anosmia, hyposmia, ageusia

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) assessed that COVID-19 outbreak could be described as a pandemic due to the alarming levels of spread and severity. In April 2020, WHO included loss of smell (anosmia) and loss of taste (ageusia) into the official list of common COVID-19 symptoms. The statistics in COVID-19 positive children and adolescents show that loss of smell and taste are common symptoms not only in adults but in pediatric patients as well and may even be the only presentation of the abovementioned infection.

AIM

The objective of the study is to review the publications subject to the problem of COVID-19 associated anosmia incidence in pediatric patients as well as its pathogenesis, diagnostics, treatment and recovery. The peculiarity of pediatric COVID-19 anosmia is due to children accounting for very low percentage of COVID-19 patients (comparing to one in adults), mostly with milder course of the disease. Awareness of anosmia and its proper diagnostics is crucial in children and adolescents, considering it can be the only manifestation in COVID-19 positive pediatric patients. That is why studying the trustworthy subject resources plays an important part in professional experience exchange for earlier detection of the disease and prevention of its further spread.

MATERIALS AND METHODS

In order to achieve this goal a meta-analysis of information from databases followed by statistical processing and generalisation of the obtained data was carried out

REVIEW AND DISCUSSION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly infective virus spread around the world that affects a considerable number of people [1]. Adults appear to play a key role in spread of the virus

in families. Transmission from a household member, often showing symptoms before them, accounted for the majority of children for whom the source of infection was identified [2, 3]. Despite this impetuous spread, the prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 in children ranges from 1-5% that is very low as compared to the total infected population [4]. Difficulty in clinical diagnostics of the disease in children due to their inability to explain their symptoms often leads to overlooking this disease. Besides, new modes of presentation, in addition to the classical telltale signs, are being reported. In this scenario, health professionals who deal with the children should be familiar with different modes of presentation of this disease in the pediatric population [1]. Nevertheless, since the initial stages of the coronavirus disease 2019 (COVID-19) pandemic, the number of infected children has grown significantly. This may be because the testing criteria for SARS-CoV-2 have changed as exposure risks, COVID-19 associated symptoms, laboratory testing capacity and priority populations evolved during the pandemic [5].

At the early stage of the pandemic, COVID-19 was primarily considered a pulmonary disease with extrapulmonary manifestations. Currently, data support that SARS-CoV-2 infection is a systemic disease with pulmonary involvement. The most frequent non-pulmonary manifestations in children were symptoms from gastrointestinal system, renal system, cardiovascular system, neurological system, lymphatic system, cutane, hepatic system, visual, gustatory and olfactory analyzers [6].

Despite children and adolescents being more susceptible to certain infectious diseases because of their developing immune system [7], COVID-19 usually has a relatively mild course in pediatric population [2, 8, 9]. Even though severe illness and death may occur [10], children and adolescents still have better incomes and lower mortality rates than adults do [11]. In children who test positive for SARS-CoV-2, the most common symptoms are anosmia and dysgeusia, nausea/vomiting and headaches in outpatients and fever in hospitalized children [11,12]. Clinical symptoms in children are not pronounced, rendering it difficult to make a diagnosis at the outset [13], among other things due to overlap with symptoms of common respiratory and gastrointestinal tract infections including abdominal pain and diarrhoea, nausea, vomiting [2, 10]. Some pediatric patients may present as asymptomatic and thus easily be missed [2].

ENT symptoms in children with SARS-CoV-2 are not specific [1]. In adults, the neck and head may be affected to varying degrees, the main symptoms being changes in taste and smell. In pediatric practice, nasal respiratory and olfactory functions are affected in different ways and various dyspeptic disorders as well as conjunctivitis and dermatitis may be associated with them [13]. In children with COVID-19, anosmia may be unaccompanied by discomfort in other organs and systems, unlike in adults [14]. Anosmia was found to be a significant predictor of a positive COVID-19 test result with positive COVID-19 reported by 75% of patients with anosmia [10]. Smell disorders (hyposmia, anosmia) occur among 15-20·% of the general population [15]. The term anosmia means complete loss of the ability to smell. In the daily clinical work, anosmia is the term used to describe the inability to smell oneself or one's surroundings. Fragments of olfaction (sense of smell) may be preserved but are generally useless in a social context. The prevalence of anosmia is 2-5% [15, 16,17]. Loss of olfactory input has several consequences: we no longer receive information about potential hazards such as smoke, fire, leakage of chemicals and poisonous substances, as well as spoiled food, leading to anxiety and stressful alertness. In addition, the smell of food is absent or distorted to such a degree that sufferers are unable to prepare and enjoy a meal. In one-third of patients, this hedonic loss gives rise to depression [17, 18]. In many cases, the patient's primary complaint is loss of taste (ageusia). The underlying mechanism is that the sense of smell adds all the subtle elements of taste beyond sour, salt, sweet, and bitter. As clinicians, we should be very aware of anosmic symptoms [19].

Postviral anosmia and chronic rhinosinusitis are two common causes of anosmia, with their pathophysiology largely being conductive, sensorineural or mixed [14]. Less common causes include nasal polyps, tumors, head trauma, chemotherapy or radiotherapy and drug-induced anosmia such as that due to tricyclic antidepressants or antipsychotics. Anosmia may recover after relief of nasal obstruction and inflammation, in addition to self-regeneration of olfactory neurons through stem cells in the olfactory neuroepithelium [14].

Smell dysfunction is known to be common in viral infections. Several viruses can cause loss of smell via inflammatory reaction in nasal mucosa, leading to rhinorrhea [19]. Common viruses associated with postviral anosmia include human coronaviruses and rhinoviruses. Edema and congestion of the nasal mucosa in the olfactory cleft causes obstruction of airflow through the nose, resulting in conductive olfactory loss. Most cases of anosmia are temporary with spontaneous recovery. Chronic rhinosinusitis may produce more prolonged anosmia or hyposmia, with predominant sensorineural inflammation and death of olfactory neurons [14]. Anosmia (and dysgeusia) can help to differentiate the diagnoses [20], as they differ significantly from the already

well-studied symptoms of reduced or lost sense of smell in patients with bacterial and viral (non-COVID-19 infection) rhinosinusitis or allergic rhinitis [21].

Higher smell or taste dysfunction rates were associated with being female, younger age, smaller sample size, patients in Asia, and with comorbidities [22].

Recent studies have shed light on the mechanisms that may underlie the loss of olfaction or gustation in COVID-19 patients [23]. SARS-CoV-2 has been found to replicate particularly well in the nose, with high viral loads detected there soon after symptom onset [32].

Angiotensin-converting enzyme 2 (ACE-2) was determined as the functional receptor for SARS-COV-2 and the organs having this receptor are targeted [24].

ACE-2 (the main host cell receptor of SARS-CoV-2) and transmembrane serine protease 2 (TMPRSS-2 a cell surface protease involved in SARS-CoV-2 cell entry) are highly expressed in a variety of olfactory epithelial cell types, raising the possibility that viral invasion of these cells may lead to anosmia [22, 25]. It has also been suggested that transcribiform viral spread and infection of more proximal elements of the olfactory pathway via central nervous system (CNS) ACE-2 receptors may also contribute to olfactory dysfunction [26]. Alternatively, it is possible that at least some of the olfactory dysfunction is conductive-secondary to nasal congestion, swelling, or inflammation preventing olfactory molecules from reaching the olfactory cleft-rather than sensorineural [27]. This may be particularly true in the subset of patients who showed improvement of their olfactory dysfunction on follow-up, although further research is needed. ACE-2 is also highly expressed on the oral mucosa and tongue, representing a potential mechanism for gustatory dysfunction [28].

As children account for less than 2% of identified cases of (COVID-19) [10], it is hypothesized that the lower risk among children is due to differential expression of angiotensin- converting enzyme 2 (ACE-2) [8]. Bunyavanich et al. conducted a retrospective examination of nasal epithelium from individuals aged 4 to 60 years during 2015-2018 [29]. The research team found age-dependent ACE2 gene expression in nasal epithelium. ACE-2 gene expression was lowest in younger children and increased with age. Linear regression with ACE-2 gene expression as the dependent variable and age group as the independent variable showed that compared with younger children, ACE-2 gene expression was significantly higher in older children, young adults and adults [29]. The same conclusion was made by Dong et al. That team also reported the reduced infection rates owing to the lower expression of ACE-2 receptors in the respiratory epithelium of the pediatric population [8].

The common feature of the patients in the researches of Concheiro-Guisan et al. and Hatipoglu et al. was that the smell and/or taste disorder developed without nasal symptoms such as nasal congestion, nasal obstruction or rhinorrhea (nasal discharge) [18, 30]. Besides, magnetic resonance interference performed on some of those patients showed no anomalies of the olfactory bulbs and tracts [30]. Given the difficulties in discriminating COVID-19 from other common pediatric upper respiratory tract infections, it is possible to use existing anosmia assessment tools alongside olfactory screening questions. These could be performed by parents or medical professionals, within primary or secondary care or even be administered remotely with instruction [17].

The "U-Sniff" is a valid and reliable method of testing olfaction in children and can be used internationally [31]. The "U-Sniff" test has been used in pediatric practice since the age of three. It is considered to be the most reliable test for detecting anosmia [12]. In Spain, for example, "Kradeo", a 7-odorant identification test, is used. The test is designed for the clinical assessment of olfaction based on the identification of familiar odorants, selected according to the cultural context and eating habits and including jasmine, mint, anise, vinegar, cinnamon, lemon and a neutral odor [18]. Reliable methods for diagnosing anosmia have been developed for children five years and older. There have been no systematic studies for children under three years of age [12]. In Japan, "Open Essence", which is a Japanese odor identification test using 12 different odor cards, is performed and it shows partially correct answers [32].

While scratch and sniff tests are widely validated and suitable for use, the unit price is likely prohibitive for mass screening. Future testing using limited panels of "child-friendly" odors, for example, mint or banana on felt-pen like dispensers and other existing multiuse tests would be suitable in a classroom setting [17]. Additionally, jellybean or 'candy smell test' have been successfully used in children: a sweet is sucked or chewed while the child blocks their nose, they then release their nose to smell the sweet's flavor, identifying one of four possible choices provided [33]. Other forms of gustatory screening using 'sweet, salty, sour and bitter' tastes or identifying sudden change in dietary preferences/altered taste could also be used [17]. The main problem is that symptoms related to taste and smell are so subjective that it is hard to assess them in pediatric age groups [34].

The visual analog scales (VAS) can be used to subjectively and easily evaluate taste and olfactory sensations [32]. In this method, the normal or usual olfactory and gustatory statuses are shown as 100%, and the current status is self-reported. In this case, we mainly used VAS

for the quantitative evaluation of olfactory and gustatory dysfunctions associated with COVID-19 over hospitalized duration to prevent nosocomial SARS-CoV-2 infection [32].

Olfaction assessment in children should combine different methods of evaluation, and not rely only on identification tasks [35]. Other assessments of olfaction sensation such as the Alinamin can also be used. The Alinamin test is performed by intravenous administration of propyl disulfide [36]. Latency, which is defined as the time between the initiation of injection and recognition of the odor (garlic smell), and duration, which is defined as the time between the recognition and disappearance of the odor, are measured. Furukawa et·al. showed that latency is influenced by olfactory acuity and duration depends on olfactory adaptation [36]. They have also reported that nonresponders to the Alinamin test had poor recovery [36], indicating that the Alinamin test can estimate the prognosis of olfaction.

Modern medicine is wary of the use of corticosteroids in the treatment of postcovid anosmia. The use of such general strengthening agents as vitamin A, zinc, omega 3 polyunsaturated fatty acids, olfactory training is recommended. If they are ineffective, two weeks after the disappearance of other symptoms of COVID-19 for anosmia, a course of topical steroids intranasally is prescribed [28].

There is a trend to quick recovery of olfactory function in children with COVID-19 [10]. The duration of olfactory and taste dysfunction varied from 2 to 15 days with anaverage of 5.7 days [37]. Olfaction and taste recover spontaneously within a few weeks, along with the resolution of other symptoms [37]. The overwhelming majority of patients have no subjective olfactory complaints by the end of the first month [38-40].

It is considered that the patients who neglect their anosmia spread the disease easily without knowing being infected, so that this symptom should be taken into consideration to detect the patients in early period [20].

To reduce the potential of person-to-person transmission, the public should be advised, if they show symptoms of new-onset anosmia or ageusia, to self-isolate and seek help from healthcare professionals. Healthcare workers attending patients with such symptoms should implement strict infection control and isolation measures to protect against COVID-19 infection in healthcare settings. Testing for SARS-CoV-2 infection is recommended for these patients [14]. The importance of anosmia should not be underestimated, as it may be the only discriminating symptom of COVID-19, so it can provide diagnostic and testing criteria for patients with no other clinical presentation to prompt early diagnostic testing in children, especially in older ones, and thereby prevent potential transmission [17, 34].

CONCLUSIONS

- Publications on COVID-19 anosmia in children and adolescents are less numerous than those concerning adult patients, so it is important to use every single trustworthy one.
- Anosmia/ageusia may be the only symptom, early identifier and the strongest predictor of COVID-19 infection in pediatric patients.
- Lower ACE-2 gene expression in nasal epithelium in children and adolescents compared to one in adults results in lower COVID-19 infection rates in pediatric population, especially in younger children.

Prospects for further scientific researches. Further researches regarding differential diagnostics of COVID-19 and other infections, including seasonal influenza, manifesting with both olfactory and taste dysfunction as well as anosmia diagnostics in children and adolescents with autistic spectrum and different types of mental disorders are possible.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions (review)

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ABSTRACT

Aim: To establish features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions.

Materials and Methods: A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic.

Conclusions: Spleen plays a leading role in the implementation of the body's defense processes, the elimination of structural elements affected by toxins, and the restoration of immune homeostasis. Its participation in the formation of the immune response can be accompanied by qualitative and quantitative changes in histological organization. Morpho-functional changes in the spleen under the action of animal venom toxins currently require careful study, because from the information available in the literature today, it is not possible to clearly construct a complete picture of lesions of certain components of the organ at the microscopic or submicroscopic levels. Therefore, this direction of research in the medical field is currently relevant, taking into account the existence of a large number of poisonous animals, including scorpions.

KEY WORDS: spleen, immune response, lymphocytes, dendritic cells, scorpion venom

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INTRODUCTION

The spleen belongs to the peripheral organs of hematopoiesis and immune response, ensuring the performance of numerous vital functions. According to the structural organization, the organ is represented by red and white pulp. It is known that the red pulp occupies a larger part of the spleen. Its main role is the careful differentiation of old, dead or opsonized blood cells that are delivered from the bloodstream to the marginal zone by terminal arterioles [1]. Despite the fact that the adaptive processes of the immune response to antigens are initiated in the white pulp, the red pulp still possesses immune effector properties. The latter consists in the fact that numerous leukocytes, including neutrophils, monocytes, and histiocytes are in the red pulp and are resident for it. The population of these cells of the myeloid line is able to undergo dynamic changes in quantity and migration under the conditions of the development of inflammatory processes, ensuring a rapid reaction of the body to an acute injury and the formation of an immune response. In addition, plasmablasts enter the red pulp from the white pulp, since there is a much higher gradient of CXCL12 chemokines (chemokines of the CXC subfamily encoded by the CXCL12 gene). Further plasma cells ensure the formation of immunoglobulins that enter the systemic bloodstream and are able to resist foreign antigens. It should be noted that CD8+ T-cells of the immune system are also present in the red pulp. They are transported here for inspection and purification, but are effector components of immune system [2].

The white pulp of the spleen is considered one of the main centers of antigen-dependent differentiation of lymphocytes. It is represented by lymphoid tissue. According to the compartmentalization of the white pulp, zones of accumulation of T- and B-cells are distinguished here. T-cell zone or periarterial zone is represented by T-lymphocytes, macrophages [3]. The last

ones provide antigen presentation and, together with interdigitate cells, participate in the antigen-dependent proliferation of T-lymphocytes. Interdigitate cells of the spleen have numerous processes that provide them with communication processes and the creation of a microenvironment for T-lymphocytes. According to their morphological structure, they are close to the cells of the mononuclear phagocyte system. It was established that under the conditions of the development of acute processes in the body, the phagocytic activity of interdigitate cells increases several times, which is accompanied by a change in their organization at the submicroscopic level towards macrophages [4, 5].

Germinal centers or B-zones are formed by B-lymphocytes, macrophages and dendritic cells. Phagocytosed antigens and their determinants in this zone are presented to T-lymphocytes, and subsequently antigen-dependent differentiation of B-lymphocytes leads to the formation of plasma cells that migrate to the red pulp for the purpose of antibody production [6].

According to the data of scientific research, concentration and clear distribution of T- and B-lymphocytes in the white pulp is determined by the presence of certain molecules in the zones. Thus, the T-zone mainly contains CCR7 (a mammalian β-chemokine receptor of the class of integral membrane proteins) and its two ligands – CCL19 and CCL21. Loss of CCR7 leads to a chaotic dispersion of T cells throughout the spleen tissue. B-zones are organized due to the presence of CXCL13 (chemokine ligand 13 or B-lymphocyte chemoattractant) [7].

AIM

The aim of the study was to establish features of immune reactivity of the spleen and mechanisms of organ damage under the influence of animal venom toxins including scorpions.

MATERIALS AND METHODS

A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When searching for information on the peculiarities of the spleen structure, the immune reactivity of the organ in response to the action of damaging factors, the influence of scorpion venom toxins on its structure and functions, we used the following combinations of keywords: «spleen», «immune response», «lymphocytes», «dendritic cells», «scorpion venom». When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic. After conducting a detailed review of the abstracts of the articles and getting acquainted with their full content, 40 sources were selected that fully corresponded to the results of the request.

REVIEW AND DISCUSSION

Violations of the normal functioning of the body under the influence of damaging factors (injuries, poisoning due to the action of toxins of various origins, viral, bacterial diseases, etc.) activate in the tissue of the spleen many PRR receptors (pattern recognition receptors) on the surface of the plasmolemma of myeloid line cells, which in turn stimulates T-cells through the presentation of antigens by macrophages and the subsequent secretion of cytokines, triggering phagocytosis. PRRs in the spleen are represented by TLRs, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs) [8]. TLRs recognize extracellular or phagocytosed pathogen-associated molecular structures (PAMPs – pathogen associated molecular patterns) [9]. A number of cytosolic NLRs are sensitive to products of microbial origin that penetrate into the cell (bacterial flagellins) and to compounds released in the host's body during trauma, stress and called molecular structures associated with damage (DAMP – damage-associated molecular patterns). CLRs act as markers for dendritic cells, helping them to recognize carbohydrate determinants and internalize pathogens (in particular, the exoskeleton of insects). PRRs are selectively expressed on the surface of different types of spleen cells, ensuring the formation of both an early and an adaptive immune response [10].

Dendritic cells (DCs) are key participants in the formation and regulation of the response of the immune defense system in the spleen. They are often the subject of discussions among representatives of the scientific community, especially regarding their classification. The reason for the differences is their special ability – dynamic and overlapping expression of T-cell markers (the possibility of production of the same markers by different subspecies of dendritic cells) [11]. According to the data research, CD4+ and CD8+ markers are known. However, other experimental findings indicate that there are a certain number of cells of the myeloid lineage that also have the properties of their expression, but they do not perform the functions of classical DCs. The discovery of specific transcription factors made it possible to understand the peculiarities of their organization and to separate them from monocytes. Splenic DCs are of bone marrow origin, with a high migration rate. Immature DCs are able to capture antigens from the bloodstream, but do not have the ability to present them and activate T cells [12]. They only

absorb antigens by phagocytosis or pinocytosis, and later undergo a multistage maturation process. Mature DCs are structures with already absorbed antigenic material. They can induce T-lymphocytes, which is accompanied by a high degree of expression of HLA antigens and other aditional stimulating molecules. In the T-zones of the white pulp of the spleen, DCs induce naïve, antigen-specific T-helpers to differentiate into type 2 T-helpers, which in turn promotes B-cell proliferation and antibody production. Classical dendritic cells (cDCs) of the spleen carry the transcription factor ZBTB46 on their surface and act exclusively as professional antigen-presenting cells [13]. They can be divided into cDC1 (classic dendritic cells 1) and cDC2 (classic dendritic cells 2) [14]. All cDC1 ensure the expression of XCR1 (X-C motif of chemokine receptors 1), which according to its chemical structure is a protein encoded by the gene of the same name and is involved in intracellular signaling processes. The vast majority of cDC1 is located in the white pulp, but is also found in the red pulp and marginal zone. cDC1 often have CD103 receptors, which are also called integrins α-E, belong to membrane glycoproteins (E-cadherin receptors). Under immunization conditions, all cDC1 activate CD8+ T cells [15].

cDC2 are located at the border of the white and red pulp, ensuring the expression of SIRPα (signal regulatory protein α) and CD11b [16]. The latter belongs to proteins of the integrin superfamily (integrin α-M), which participates in the processes of interaction between monocytic cells, mediates the absorption of particles opsonized by complement, as it recognizes the sequence of C3b amino acids. In addition, CD11b is a receptor for fibrinogen, factor X, ICAM-1 [17].

Some experimental models demonstrate the presence of atypical DCs in the spleen. They are identified using receptors B22a (CD45R – signaling molecules necessary for the activation of T cells and are members of the tyrosine phosphatase family) and PDCA-1 (plasmocytoid dendritic cell antigen-1) [18]. Atypical DCs carry TLR7 and TLR9 on the surface of the plasmalemma, which enables them to identify pathogens, including viruses. After activation, these cells extremely quickly secrete large amounts of type I interferons, IL-12, IL-18, increase the levels of NK cells, stimulate apoptosis of infected cells, enhance cross-priming (induction of naïve CD8+ T cells and their transition into activated cytotoxic cells). Cross-priming allows DCs to involve in the antigenic presentation of exogenous antigens class I MHC molecules (usually they do not participate in these processes). The use of class I MHC allows DCs to remain uninfected, providing an immune response by activated cytotoxic T-lymphocytes against the affected body cells [19].

Macrophages in the spleen, which are resident cells, are involved in the protection of the tissue of the organ, as they provide phagocytosis, maintenance of homeostasis, cleaning from remnants of apoptotic material, and regulation of the function of neighboring cells. They also respond to damage, stress, or infection by stimulating the production of numerous cytokines and activating leukocytes [20]. Several types of macrophages have been identified in the spleen, each of which is responsible for the normal functioning of individual anatomical structures and expresses its own types of PRRs and scavenger receptors (SRs). [21]. In particular, in the marginal zone, marginal zone macrophages – MZM and marginal metallophilic macrophages – MMM are distinguished. Both types are characterized by the expression of SIGN-R1 and CD169 (sialoadhesins) [22]. The last ones play an important role in the detection and absorption of microorganisms containing residues of sialic acids. The aforementioned macrophages are involved in cleansing the spleen of cells that have undergone apoptosis. It has been established that MZM and MMM are of bone marrow origin and are important for the induction of immune tolerance to MHC self-antigens. In the bone marrow, they mature under the influence of the macrophage colony-stimulating factor, since they have common features of ontogenesis with blood monocytes [23, 24].

The scientists note that there are currently available data on the participation of NK cells in the innate and adaptive immune response of the spleen. The vast majority of these cells are concentrated in the red pulp, however, they can migrate to the white pulp under conditions of infection, contribute to T-lymphocyte polarization, TNF-α production, and DCs differentiation [25]. NK cells protect against viral infections (due to the presence of PRR), are involved in the recognition of tumor and damaged cells of the body. The latter fact is possible due to the expression of NKG2D, which is a transmembrane protein of the superfamily of C-type lectins, and its levels on the surface of the plasmalemma increase under the influence of such cytokines as IL-15, IL-12, and IFN-γ. This receptor is responsible for the detection and elimination of transformed, dead cells, since its ligands are induced as a result of infection, damage or genomic stress [26].

Under normal conditions, monocytes are also present in the spleen tissue. There is information in scientific sources that, as a rule, monocytes after interaction with foreign agents in the blood are able to penetrate the marginal zone of the spleen and stimulate the activity of resident macrophages. Also known are the effects of monocytes, such as disposal of cells that have undergone apoptosis, stimulation of TGF-β, IL-10 production. During the development of an inflammatory response, chemokine receptors β (CCR2), activated by cytokines MCP-1 and MCP-3, recruit monocytes from the red bone marrow to the spleen. Further, they can differentiate into several types of

cells of the myeloid lineage, including non-classical DCs. It should be noted that the red pulp of the spleen acts as a so-called depot for undifferentiated monocytes, which can be involved in the processes of immune reactivity in other organs [27].

The adaptive immune response in the spleen is provided by T- and B-cells, which belong to the key effector structures of the organ. Their localization may change depending on the functional state. B cells are canonical T-dependent immunoglobulin-producing cells. The so-called naïve B-lymphocytes are localized in the follicles of the white pulp, however, after activation, they are able to move within the light and dark zones of the germinal centers. Chemokine receptors of the fifth type (CXCR5) direct the movement of B cells to the light zone, where they interact with T cells [28], and receptors of the fourth type (CXCR4) direct them to the dark zone, where B lymphocytes undergo proliferation [29].

CD4+ T cells concentrate on the outer border of the periarterial lymphoid sinuses, next to the follicles. Their function is to stimulate the synthesis of antibodies by B-lymphocytes (high-affinity antibodies) due to the production of specific cytokines (IL-21) and direct co-stimulation. Often this type of cells is called T-follicular helpers. During the activation of the immune response, CD4+ increase the expression of CXCR5 so that B cells can quickly reach the T-B border. B-lymphocytes, in turn, under these conditions actively express β-chemokine receptors (CCR7) [30, 31].

CD8+ or naïve T lymphocytes reside in the central compartments of the periarterial lymphoid sinuses of the white pulp of the spleen, awaiting antigenic presentation. After priming, activated cytotoxic T-cells migrate through the B and marginal zones, reaching the red pulp, where they are involved in the processes of destroying infected cells and cleaning the tissue of the organ. Over time, individual memory T cells return to the sites of primary localization. However, some memory T cells still remain within the red pulp [32, 33].

The analysis of scientific publications made it possible to establish the fact of the existence of hybrid cells in the spleen or innate lymphocytes. One of the most common are NKT cells and γδ T cells, which belong to specialized structures, express the TCR receptor and are able to recognize glycolipid antigens on the surface of antigen-presenting cells, such as MZM [34]. Activated NKT cells produce proinflammatory cytokines and can stimulate DCs to cross-priming of CD8+ T lymphocytes. γδ T cells also possess the properties of rapid cytokine secretion, PRR expression, and direct lysis of infected cells. They are a minor population in the spleen, but are important for the early immune response. NKT and γδ T cells are required for Th1 polarization. This process is possible due to the production of IFN-γ, TNF-α, IL-12, which also activate cDC1 [35, 36].

Another type of hybrid spleen cells are innate lymphoid cells (ILCs). They got their name due to the fact that they are characterized by a common ontogenesis with cells of the lymphoid line, but unlike them, they do not have T-cell receptors [37]. Currently, several types of ILCs are known, their classification depends on the profile of cytokine secretion. The last ones are produced by them in response to damage or infection. ILC-2 produce IL-5, IL-9, IL-13. ILC-3 are able to activate cells of the marginal zone of the spleen, neutrophils through the production of TNF-α, lymphotoxin, GM-CSF and provide costimulation processes of CD4+ T cells in interaction with IL-2, IL-6, macrophage inflammatory protein 1-α (MIP1α) [38].

According to experimental research, the components of scorpion venom have a pronounced effect on the structures of both innate and acquired immunity. Today, more and more frequent studies are devoted to the study of morpho-functional changes in immune defense organs during bites of poisonous animals. Scientists show considerable interest in histological and biochemical changes of the spleen under the influence of zootoxins. The systematization of information from scientific sources made it possible to reach a conclusion about the high sensitivity of the spleen to the action of factors of various genesis. Scientists believe that knowledge of the histological indicators of this organ, as special biomarkers, will allow a better understanding of the integral impact of the environment on the human body. In scientometric databases, an extremely limited amount of information was found on the effect of scorpion toxins on the structure of the spleen of mammals [39]. The vast majority of experiments are devoted to the study of its participation in the development of inflammatory processes during bites of poisonous animals. There are also few reports on this issue. Thus, Costa-Arce J. et al. [40] established that the venom of Centruroides limpidus scorpions leads to an increase in the production and secretion of IFN-γ, IL-4, IL-17, IL-10 in the spleen of mice by T-helpers. The authors proved that most of the toxins that had such an effect belong to blockers of potential-dependent Na+ and K+ channels. To implement their pathological effects, they use the specified T-lymphocyte channels as molecular targets. The researchers also concluded that these toxins were not active in the proliferation of T-helper cells in the spleen.

CONCLUSIONS

As stated above, the spleen plays a leading role in the implementation of the body's defense processes, the elimination of structural elements affected by toxins, and the restoration of immune homeostasis. Its participation in the formation of the immune response can be accompanied by qualitative and quantitative

changes in histological organization. Morpho-functional changes in the spleen under the action of animal venom toxins currently require careful study, because from the information available in the literature today, it is not possible to clearly construct a complete picture of lesions of certain components of the organ at the microscopic or submicroscopic levels. Therefore, this direction of research in the medical field is currently relevant, taking into account the existence of a large number of poisonous animals, including scorpions.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Abuse of right during application of coercive medical measures in criminal proceedings

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ABSTRACT

Aim: To determine the problematic issues of ensuring the rights and freedoms of persons suffering from mental disorders and to whom CMM are applied in criminal proceedings under the legislation of Ukraine and the legislation of the states that adhere to the modern concepts of international standards of human rights ensuring to a person the CMM are applied to

Materials and Methods: Legal positions of the ECHR, criminal procedural legislation of a number of states, and a survey of scientists and practitioners conducted by the authors are used in this paper (total number of respondents was 168). A set of general scientific and special methods are used to achieve the aim of the study.

Conclusions: The practice of applying CMM to persons suffering from mental disorders in criminal proceedings in Ukraine and other states does not fully meet international standards and needs improvement. It was suggested to make changes to the legal acts on the use of CMM in criminal proceedings.

KEY WORDS: criminal proceedings, mental disorders, coercive medical measures, abuse of rights, the practice of the European Court of Human Rights, collisions and gaps in legislation

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INTRODUCTION

Applying coercive medical measures in criminal proceedings requires detailed legal regulation, as they apply to persons who have committed a socially dangerous act and suffer from mental disorders. However, according to the legislation of Ukraine and other countries, the legal regulation of criminal proceedings in which issues regarding the application of CMM to persons needs improvement. Although the legislators in all states, without exception, justifiably provide such persons with additional procedural guarantees, in some countries, particularly in Ukraine, these persons are deprived of certain rights, including limited opportunities to defend their interests independently in criminal proceedings, which does not comply with the European Convention on Human Rights (hereinafter – the Convention).

AIM

The paper aims is to determine the problematic issues of ensuring the rights and freedoms of persons suffering from mental disorders and to whom CMM are applied in criminal proceedings under the legislation of Ukraine and the legislation of the states, which correspond to the modern concept of international standards for ensuring the rights of persons to whom the CMM applies; to highlight and analyze the ECHR's key positions in the context of respect for the right to liberty and security of person (Article 5 § 1 (e) of the European Convention on Human Rights (hereinafter – the Convention) in criminal proceedings concerning the use of CMM; to suggest proposals for improving Ukrainian legislation and the legislation of the states that adhere to the modern concepts of international standards of human rights ensuring to a person the CMM are applied to; to minimize situations in which the rights and legitimate interests of persons with mental disorders may be unreasonably limited.

MATERIALS AND METHODS

The study is based on scientific works concerning medical law and criminal procedure. The normative basis of this work is the legal acts of a number of states that profess modern legal values and are based on the concept

of human rights. The criminal procedural legislation of Ukraine, which is intensively developing and improving, in particular, in connection with the tasks that have arisen due to the future accession of Ukraine to the European Union, was taken as bases. The legislation of other states that have achieved success in regulating the application of CMM was used for comparison and taking into consideration the best practices, in particular, the Republic of Moldova, the Republic of Armenia, the Republic of Estonia, the Republic of Azerbaijan, the Republic of Kazakhstan, the Federal Republic of Germany, the Czech Republic and Canada. In addition, during this study, the relevant practice of the ECHR and some resolutions of the UN General Assembly were analyzed.

In the preparation of the article, a complex of philosophical, general scientific and special scientific methods of scientific knowledge was applied in connection. The basis of the analysis is the method of idealistic dialectics, as a fundamental philosophical method of scientific research, with the use of which the application of CMM is considered as a dynamic phenomenon that is in constant motion, development and is characterized by a complex of interrelated elements, which together constitute a complex and systemic phenomenon. Observance of civilized principles of justice and realization of human rights for all participants in the process is an indispensable component of legal regulation and application of the CMM. At the same time, in the study of the given problem, general scientific methods were used, including observation and counting (for collecting empirical data and calculating quantitative results, in particular, surveying respondents and materials of law enforcement practice), abstraction (for imaginary departure from insignificant differences in the legislation and law enforcement practice of individual states and selection of essential features that determine the essence of the CMM and its difference from related institutions, as well as law-making decisions and law-enforcement positions), induction (to establish the characteristic features of the application of the CMM from the point of view of observing human rights), analysis and synthesis (thanks to the use of this method, the application of the CMM is considered as a holistic phenomenon and, at the same time, as a component of the application of other legal means), systemic (the use of which made it possible to consider the elements of the CMM application and the connections between them), idealization (to build an ideal an impeccable model of the application of the CMM, which includes the best elements of all the national models taken for comparison and study). In addition, special scientific research methods were used, which is legal in its content. Among them: the dogmatic method (thanks to which the content of legal norms and law-enforcement positions was established), the method of comparative jurisprudence (for comparing the common and different in the legislation of individual states), legal forecasting (the use of this method made it possible to predict how the proposed changes to the legislation will be applied in practice and will ensure compliance with human rights and the ideals of modern justice). These and other methods were used in their relationship and mutually complement each other.

REVIEW AND DISCUSSION

Peculiarities of conducting criminal proceedings against persons with mental disorders are fixed at the level of international legal acts. Despite this, in the legislation of some countries, the legal provisions regulating the procedure for applying CMM in criminal proceedings are formulated in contradiction or incorrectly with each other. It, in turn, gives grounds for the subjects conducting the criminal trial to abuse the rights granted to them, using them not for their intended purpose but contrary to the tasks set before these subjects in the criminal trial. Great attention is paid to the issues of ensuring the rights and legitimate interests of persons who have committed acts prohibited by the national Criminal Codes, being partially sane, insane or who fell ill with a mental illness already after committing a criminal offence and to whom the question of the application of CMM is being decided [1-3]. However, we have to state that the legal regulation of proceedings conducted against such categories of persons needs to be improved to prevent dual interpretation of the relevant norms by law enforcement authorities since it leads to a restriction of the rights of these participants in the trial. Sometimes it is difficult or almost impossible to criticize such limits directly. Still, they are committed to evading the persons conducting the criminal trial from fulfilling their duties, resorting to this to reduce the workload or for other illegal reasons. Such behavior, under certain conditions, is an abuse of rights. Still, it is impossible to bring these persons to one or another type of legal liability due to the absence of direct prohibitions violated by them. Thus, by abusing the right, a person exercises the right granted to him under the clearly defined limits of the law. Still, at the same time, he exercises this right in the absence of or contrary to his interest and the purpose of the right itself. In this case, there is no expressed illegality in the behavior of such a person. Such behavior formally "fits" into the framework of the law and only creates a semblance of legality. Therefore, as an excuse, pre-trial investigation bodies or judges can always refer to the fact that at least

one of two or more conflicting regulatory acts/one of the provisions of the same act, between which there are disagreements and contradictions, yet gives them such an opportunity.

Such a conclusion is the result of a questionnaire conducted by the authors of the article. We conducted a survey among representatives of the legal professions from Ukraine (lawyers, prosecutors and judges), representatives of juridical higher educational institutions from Ukraine and from other countries, such as: the Republic of Moldova and the Slovak Republic, as well as medical staff of regional and district centers from Ukraine. It was conducted to find out the opinion of individual representatives of the legal and medical professions about the reasons for the possible abuse of procedural rights in the criminal proceedings within applying the CMM. The survey was conducted during April - July 2023, through an anonymous questionnaire using Google Forms (the total number of respondents - 168, 40.5% of which at the age of 20 to 35, 50% - of 36 to 45, and 9.5% - of 45 to 65; out of all 83.33% hold a position related to legal professions, the rest 16.77% - medical staff; among the respondents – 23.38% are persons whose work experience in the relevant specialty is more than 20 years, 29.76% are persons, whose work experience is less than 10 years and 46.86% - persons with work experience from 10 to 20 years). Thus, 90.5% of the participants in the questionnaire, conducted by the authors of the article, claim that the main reason for the abuse of procedural rights in criminal proceedings on the application of the CMM (both by private participants in criminal proceedings and by bodies conducting criminal proceedings) is unclear legislative regulation. A slightly smaller number of respondents (82.14% out of all respondents) indicate that abuse of rights by participants in such criminal proceedings may have a negative impact on its course and results.

Both legislation and law enforcement practice in the field of mental health care need improvement and development, taking into account the recommendations and experience of international organizations, relevant state bodies and institutions, and the positions of practical workers. Inadequate legal protection of persons to whom the issue of the application of CMM is being decided, as well as the possible highly negative consequences of the illegal and unjustified application of these measures for the health, reputation and further fate of persons, precisely determine the undoubted relevance of the topic itself and the attention of researchers to it.

1. PROBLEMS OF PROTECTING THE RIGHTS OF PERSONS WITH MENTAL ILLNESS IN CRIMINAL PROCEEDINGS.

The Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care, adopted by the United Nations General Assembly, state the need for priority study of the issues of protection of persons to whom proceedings are being conducted to apply CMM in connection with the presence of mental illness[4]. That is why developing effective mechanisms for protecting the rights of persons with mental disorders in criminal proceedings is one of the most relevant scientific directions. In this context, the case-law practice of the ECHR concerning the lawful detention of persons with mental illness in accordance with subparagraph "e" of Article 5 §1 of the Convention (The lawful detention of persons of unsound mind) becomes of great importance. Deprivation of the right to freedom and personal inviolability of individuals with mental illness is considered lawful in compliance with three conditions, which the ECHR first established in the case of *Winterwerp v. the Netherlands*[5]:

1) if the person is reliably proven, by the opinion of a medical expert, to be of unsound mind;

2) the deprivation of liberty must be proven to have been necessary for specific circumstances, i.e. mental disorder is such that the person is forced to be kept in a psychiatric hospital;

3) the mental disorder, confirmed by the necessary medical evidence, must persist throughout the period of detention (persistence of mental illness).

Based on the analysis of the case-law practice of the ECHR, a fourth criterion can be identified – a particular connection must be proven between the reason on which the decision to deprive of liberty is based and the place and conditions of detention. Theoretically, the "detention" of a person as a mental-health patient will be "lawful" in the sense of subparagraph "e" of Article 5 §1 of the Convention only if it is effected in a hospital, clinic or other appropriate institution authorized for that purpose. Such persons should not be kept in prisons where proper treatment and care are unavailable[6]. It is important to note that according to the case-law practice of the ECHR, the requirement of placement of mentally ill persons in an institution suitable for the detention applies both to preventive detention (stay in custody) and to the length of a term of imprisonment[7] (Case of *W.A. v. Switzerland*).

1.1. A person's right to be acquainted with a request to apply coercive medical measures. It must be stated that in the legislation of Ukraine, there are many contradictory provisions, which lead to violations of the rights of persons to whom the question of application of CMM is being decided or has already been applied. An example of a contradictory legislative regulation, which allows the abuse of rights by professional participants in

criminal proceedings, is the provision of part 1 of Article 293 of the Criminal Procedure Code (hereinafter – the CPC) of Ukraine[8]. Accordingly, a copy of the petition for applying CMM is handed over only to its defender. At the same time, part 2 of Article 317 of this Code states that the participants in the court proceedings (which, of course, include the person to whom the issue of the application of the analyzed measures is being decided) should be allowed to familiarize with the materials of the criminal proceedings, subject to a request for this. However, to make such a request, the participants in the criminal trial must be aware of: 1) that the proceedings are being conducted for them, 2) for what reasons they were involved in it, and 3) their legal status. At the same time, it is impossible to do this thoroughly without first being acquainted with the request to apply CMM to them.

Therefore, it seems that since the person against whom the proceedings are being conducted is not indicated in the list of persons who are provided with copies of the petition for the application of CMM and the register of materials of the pre-trial investigation, the prosecutor may not provide such documents to him without violating the requirements of Article 293 the CPC of Ukraine. However, it does not ensure the right to protection of such a person, which is directly established as the basis of criminal proceedings. In addition, 64.28 participants of survey participants agree with the conclusion of the paper's authors.

In this regard, the approach is reflected in the CPC of several states, such as in clauses 1, 11 and 13, part 1, part 2 of Article 515, part 2 of Article 518 of the CPC of Kazakhstan[9], part 2 of Article 570, part 3 of Article 459 of the CPC of the Republic of Moldova[10], Article 456 of the CPC of Armenia[11], Article 473 of the CPC of Azerbaijan[12] (the positive experience of which should be adopted by the Ukrainian legislator as well), where the person to whom the issue of the application of CMM is being decided is called an independent subject (along with his defender and legal representative) of the right to familiarize himself with all the materials of the criminal proceedings.

1.2. The right of a person to give testimony and its probative value.

Concerning the normative regulation, the participants conducting the criminal trial may limit the exercise of the right of persons with mental disorders to defend their rights and legitimate interests regarding the independent defense of their claims by ensuring only the formal presence of such persons, do not allow them to express considerations and arguments regarding the circumstances of the investigated act. The legislator provides a hypothetical opportunity for these abuses due to the inconsistency of some norms of the CPC of Ukraine.

Thus, part 1 of Article 512 of the CPC of Ukraine states that the criminal trial is carried out with the mandatory participation of the natural person to whom the issue of the application of CMM is being resolved. Under the provisions of clause 5, part 3 of Article 42 and part 1 of Article 506 of the CPC of Ukraine, a person has the right to give testimony and explanations to the extent determined by the nature of the disorder of mental activity/mental illness. However, the procedure for interrogating the participants in the criminal trial was not mentioned in the domestic CCP, and the status of evidence was never given to the testimony, explanation or other information provided by such a person. It must be stated that similar shortcomings of legal regulation occur when the legislator formulates the relevant provisions very half-heartedly and inconsistently. Because on the one hand, it seems that the legislator allows such subjects to express their position in the form of testimony or explanations (clause 4, part 2 of §398 of the CPC of Estonia[13], Article 456 of the CPC of Armenia[11], Article 473 of the CPC of Azerbaijan[12], clause 3 of §415 of the CPC of Germany[14]), but does not give it probative value, which is also characteristic of other countries.

This approach goes counter to the provisions of the UN General Assembly Resolution "The Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care"[4], according to which the patient can be entitled to attend, participate and be heard personally in any hearing. In addition, such a situation contradicts the provisions of Article 6 of the Universal Declaration of Human Rights (hereinafter – the UDHR) of December 10, 1948, which states that everyone has the right to recognition everywhere as a person before the law[15]. Many researchers (including 84.52 of the participants in the questionnaire conducted by the paper's authors) come out in favor of such persons being interrogated about the circumstances of the committed illegal act. After all, the person against whom proceedings are being conducted regarding the application of CMM enjoys the rights of a suspect/accused, one of which is, in particular, the right to testify. In addition, supporters of the possible interrogation of such persons and the provision of information with probative value (the paper's authors are among them) refer to the decisions of the ECHR (Case of *I.N. v. Ukraine*"[16], and Case of *D.R. v. Lithuania*"[17]. The Court drew attention to the importance of the formal presence of a person with mental disorders at court hearings and, if possible, his active participation in criminal proceedings (if his mental state allows it and

he wants to do it). Given the above case-law practice of the ECHR, Ukrainian courts usually provide such a participant in the proceedings with the opportunity to take part in the trial and sometimes even listen to him in criminal proceedings, and the information he provided is recorded in the relevant decisions.

However, this approach seems insufficient because, from a legal point of view, these are not identical things: 1) give a person the opportunity to express his position in the proceedings and 2) provide the information reported by him with probative value. He can use the information for his defense, evidence of non-involvement in the investigated act, and law enforcement officers – to propose new theories of the investigated act and their verification. Because of this, the provisions of the criminal procedural laws of Ukraine, Estonia, Uzbekistan, Kazakhstan, Germany and Armenia should be formulated in such a way that there is no doubt that the testimony of the person against whom the proceedings regarding the application of CMM are being conducted is one of the procedural sources of evidence.

In addition, here, it is also worth noting that the necessity of conducting a trial with the mandatory participation of the person to whom the issue of the application of CMM is being decided is due to the provision of his right to give testimony and explanations for his defense. The right to defense includes the ability to defend oneself by all means and methods, both proscribed and not proscribed by law, but do not contradict it. However, this in no way means that the person to whom the issue of the application of CMM is being resolved has the right to testify against a person known to him to be innocent of the commission of a criminal offence by him. Such a protection method will violate an innocent person's legitimate rights and interests, which goes against the norms established in international legal acts. Therefore, every person is obliged not to infringe on or violate other people's rights and freedoms. Accordingly, the right to defense is limited, and its implementation cannot violate the rights and interests of others. One of the methods, which is not directly prohibited by the legislation of Ukraine and can be used to exercise a person's right to defense, is a false report about the commission of a criminal offence by a knowingly innocent person. For example, it is a penal act in the Federal Republic of Germany. However, false reporting appears to infringe on the rights of another (innocent) person and is inherently an abuse of the right to defense.

1.3. The right of a person to appeal a decision on the application of CMM. The right of a person to appeal a court decision is one of the components of the right to a fair trial, guaranteed by Article 6 of the Convention. The absence of provisions in the criminal procedural law that ensure the right of the person to whom the issues of applying CMM are being resolved makes the possibility of personally appealing the decisions concerning this person inadmissible. Despite this, such norms are enshrined, particularly in clause 5, part 1 of Article 393 and clause 5, part 1 of Article 425 of the CPC of Ukraine. Accordingly, the person to whom the question of the application of CMM was decided independently (without the assistance of a defense attorney or legal representative) cannot appeal the court decision in the appeal and cassation procedure. This approach seems unreasonable. Every person shall be deemed not to have a mental disorder until such a disorder is established in the manner prescribed by law. Only when the court's decision on applying the specified measures enters into legal force such a presumption is refuted. In addition, not every disorder of mental activity automatically indicates a person's unfitness to plead[18, 407 – 410].

In this regard, the approach of the legislator of some states is justified. Accordingly, the independent subject of the right to appeal and cassation of court decisions is the person to whom the issue of the application of CMM is being resolved (clause 6, part 1 of Article 401, Article 421 of the CPC of the Republic of Moldova[10], Article 376 of the CPC of the Republic of Armenia[11], part 1 of Article 318 and part 1 of Article 344 of the CPC of Estonia[13], clause 1, part 4 of Article 383, clause 1.4 of Article 409 of the CPC of the Republic of Azerbaijan[12]). Therefore, the person to whom the issue of the application of CMM was decided has the right to independently file an appeal and a cassation complaint against the court's decision, which concerns his interests. This position, defended by the paper's authors and supported by 60.71 participants of the survey conducted by the authors, is entirely consistent with several decisions of the Court, such as *Anatoliy Rudenko v. Ukraine*»[19] and *Plakhteev and Plakhteeva v. Ukraine*[20].

2. PROBLEMS OF LEGAL REGULATION OF CONTINUATION, MODIFICATION AND TERMINATION OF APPLYING CMM.

It must be stated that in the legislation of various countries (Article 95 of the Criminal Code (hereinafter – CC) of Ukraine, part 3 of Article 19 of the Law of Ukraine "On Psychiatric Assistance"[21], part 2 of Article 514 of the CC of Ukraine[8], §403 of the CC of Estonia[13], part 1 of Article 503 of the CC of the Czech Republic[22], Article 672.22 of the CC of Canada[23], part 4 of Article 523 of the CC of Kazakhstan[9]) the grounds for the court's adoption of a decision on changing and terminating the application of CMM are vaguely formulated. Unfortunately, the analysis of the provisions of the CC

and the CPC of the specified countries does not make it possible to confidently and unequivocally prove that the grounds for termination of applying CMM or amendment to a less strict type cannot be a significant deterioration of the patient's mental state, for which he is objectively unable to cause any damage. In addition, the provisions of the specified legislative acts of some countries do not provide grounds for a definite conclusion about whether it is possible for *a change in the physical condition* of a person to whom the issue of applying CMM is being decided to be a reason for terminating their application or changing them to more or less strict ones.

Quite often, the legislators of foreign countries, speaking about changes in the state of health of a mentally ill participant in criminal proceedings, do not specify whether such changes are related to improving health and ignore whether they concern only mental or physical health.

The researcher V. Navrotska claims that the change of a coercive medical measure to a less severe one or the termination of the use of such a measure can be caused by a significant deterioration of the mental state of the patient, as a result of which his social danger becomes extremely low, sharply decreases (sometimes so much that the vital activity of such persons without third-party care becomes impossible) [24]. A similar situation can happen, for example, with the development of senile dementia in a mentally ill person, the progression of profound dementia.

The decision to change CMM to a less severe one or to stop its use can be made even if only *the physical health* of a person with a mental illness changes (61.9% of the respondents interviewed by the paper's authors agree with this statement). Such a decision can be made in the case when, according to the conclusion of the therapist, the patient's life, to whom the specified measures were previously applied, is not possible without third-party care or is very complicated (for example, a mentally ill person fell into a coma or he developed complete paralysis) and because of this he is not capable of harming either others or himself. CMM can be applied only to those persons with mental disorders who are *socially dangerous*. Therefore, if the person to whom such measures were applied, over time, ceased to be dangerous to himself and/or others (and the paper's authors are convinced that from the point of the law, it should not matter whether the loss of this danger occurred as a result of changes in the mental state or physical health, as well as the nature of these changes), then such measures should be terminated. If, after the decision to stop the use of CMM, the person's mental illness/mental disorder (who has ceased to be socially dangerous) has not yet passed, and because of this, he needs further psychiatric treatment, then the relevant decision can be made at the request of interested persons in civil proceedings.

A situation in which a decision to modify a coercive medical measure to *a stricter type* (de lege ferenda) could be based on only changes in a person's physical health (when the mental disorder remained unchanged) also appears to be acceptable. For example, for a wholly paralyzed insane person, the court admitted him to a psychiatric institution with regular supervision. The patient's physical condition may improve significantly in the future because of proper treatment and care. His motor activity will be fully restored (theoretically allowing him to continue committing illegal acts), but the level of aggressiveness caused by the mental disorder has not changed. Therefore, it is more likely that such patients will cause harm to public goods, and it is necessary to apply stricter CMM to them.

Incidentally, we note that in its practice, the ECHR considers the deprivation of liberty of a mentally ill person legitimate when not only such a person needs treatment but also when he needs control and supervision to prevent harm to himself or others, i.e. the social danger of such a person is taken into account. In the case *Strazimiri v. Albania*[25], ECHR emphasized that irrespective of the facility in which those persons are placed, they are entitled to be provided with a suitable medical environment accompanied by actual therapeutic measures, with a view to preparing them for their eventual release. Regarding the amount of treatment provided, the ECHR considers that the level of care required for this category of detainees should go beyond basic care.

In turn, in the practice of the ECHR, mentally ill persons enjoy the guarantee of mandatory periodic review of the decision on the continuation of compulsory treatment in special psychiatric institutions. In such cases, the ECHR establishes whether the decision of the national courts to continue the forced deprivation of a person's liberty was based on relatively new expert opinions (sufficiently recent). In the case *Miklić v. Croatia*[26], the ECHR established a violation of the rule of paragraph 1 of Article 5 of the ECHR due to non-compliance with the procedure for deprivation of liberty established by law. As was found out in this case, the domestic courts ignored the applicant's request, who had previously been diagnosed with mental disorders, to obtain a new opinion from an independent expert. In particular, the special procedure established by Article 37(2) of the National Law on the Protection of Persons with Mental Disorders was not observed. Accordingly, when deciding on the periodical prolonging of the

period of the forced internment of a person at the motivated request of the relevant person, the national court, as a rule, is obliged to obtain a new expert opinion from a person who does not work in the relevant institution. In similar cases, the ECHR stresses that the possibility for patients to obtain a different opinion from independent psychiatric experts is a principle that is also included in the UN Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care. It is an essential guarantee against possible arbitrariness when deciding whether to continue compulsory treatment (Case of *Anatoliy Rudenko v. Ukraine*) [19].

CONCLUSIONS

The mechanism for ensuring the rights of the person to whom the issue of applying CMM is being decided needs improvement. The legal regulation of criminal proceedings conducted against such persons leads to the abuse of their rights by participants in criminal proceedings. Therefore, to avoid such abuses, it would be necessary to improve the procedure for acquainting these persons with the materials of criminal proceedings to provide for their right to appeal court decisions on the issue of the application of CMM and to regulate the procedure for giving testimony and explanations by such persons.

One of the effective ways to protect persons who suffer from mental disorders would be to avoid law enforcement errors and prevent the abuse of rights in criminal proceedings. For this purpose, it is necessary to eliminate contradictions in the provisions of the Criminal Procedural Code of Ukraine and in the procedural codes of other states and improve law enforcement practice in this area. To this end, we suggest that in the legal acts of the states that adhere to the modern concepts of international standards of human rights ensuring to a person the CMM are applied to, provide:

- the provision that, simultaneously with the submission of a petition for the application of CMM to the court, the prosecutor is obliged to file a copy of it and a copy of the register of the criminal proceedings materials to the person to whom the question of the application of CMM is being decided;
- a norm that would regulate the procedure of interrogation of the person to whom the question of the application of CMM is being decided;
- the right of a person to whom the question of the application of CMM is being decided to appeal the court's decision on the application of CMM.

At the same time, in the course of the analysis of the problems of legal regulation of the continuation, modification and termination of the application of CMM, conclusions were drawn:

- improvement of the mental state of the patient is not mandatory for stopping the use of coercive medical measures or changing them;
- such a change in a person's mental state is sufficient for changing or stopping the use of CMM, as a result of which his potential danger is reduced in the event of a deterioration of his mental state, which results in the loss of the ability for conscious volitional behavior. Such a decision can also be made in case of a change in the physical health of a mentally ill person, although the mental disorder has remained at the previous level;
- deterioration of the patient's mental state should not always be the reason for the appointment of a stricter CMM. The social danger of the person should be decisive (in case of its growth, a stricter type of CMM should be applied, and, conversely, when the danger is reduced, a softer type of them should be applied);
- when deciding to continue the use of CMM, it is necessary to take into account the lack of positive dynamics of a mental disorder, the data on the mental state of the person at the time of the study, the forecast of experts, in which the specialists consider the stability of the effect obtained from the compulsory treatment and the possible course of the mental disorder.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

D-hormone and its significance for function of prostate gland (literature review and personal observations)

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ABSTRACT

Aim: The aim of this article is to present literature data and personal research of the role of D-hormoneon the functioning of the male reproductive system, and more specifically of the prostate gland, as well as the use of this vitamin D during the complex and independent treatment of benign prostatic hyperplasia in preclinical studies and clinical practice.

Materials and Methods: The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on reproductive endocrinology and pharmacology sources were also conducted for related published studies . Selected keywords ("benign prostatic hyperplasia" OR "BPH") AND ("prostate") AND ("reproductive system and vitamin D") were used to collect data. The article also presents our personal data of preclinical studies and clinical data of the use of vitamin D as monotherapy and in the complex therapy of reproductive disorders.

Conclusions: The effect of vitamin D on prostate volume and BPH has shown perspective results, therefore, it is proposed to conduct further studies on the role of vitamin D in the formation of BPH and reproductive disorders, their prevention and treatment. The use of vitamin D as monotherapy or in the form of pharmaceutical compositions and its inclusion in basic treatment regimens can increase the effectiveness of the prevention and correction of reproductopathies in the presence of or due to BPH and suggests the possibility of restoring the generative potential of individuals with BPH, both with and without D-hypovitaminosis.

KEY WORDS: vitamin D , reproductive system, benign prostatic hyperplasia

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INTRODUCTION

It is known that the number of patients with benign prostatic hyperplasia (BPH) is increasing. It is estimated that BPH occurs in an average of 80% of men after the age of 60. However, under the influence of the rapid aging of the population, dynamic pace of life, stress and the effects of harmful environmental factors, BPH has become an important health problem worldwide. The researchers' search is focused on finding substances for the treatment of BPH among natural medicines as an adequate alternative, devoid of the main disadvantages of systemic prostatoprotectors. prevention and treatment of diseases of the prostate gland has not only medical, but also social significance. A prostatogenic decrease in fertility can have various causes, which are more often associated with a violation of the structure and function of this gland. One of the current problems is the study of the effect of D-hormone on the body, and in men its effect is closely related to the pathogenesis of androgen deficiency and hypofertility.

AIM

The aim of this article is to present literature data and personal research of the role of D-hormoneon the functioning of the male reproductive system, and more specifically of the prostate gland, as well as the use of this vitamin D during the complex and independent treatment of benign prostatic hyperplasia in preclinical studies and clinical practice.

MATERIALS AND METHODS

The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on reproductive endocrinology and pharmacology sources were also conducted for related published studies . Selected keywords ("benign prostatic hyperplasia" OR "BPH") AND ("prostate") AND ("reproductive system and vitamin D") were used to collect data. The article also presents our personal data of preclinical studies and clinical data of the use of

vitamin D as monotherapy and in the complex therapy of reproductive disorders.

REVIEW AND DISCUSSION

It is well known that the prostate affects fertility and any pathological processes in it affect the male reproductive system. The prostate gland produces a secret that makes up 25% of the volume of seminal fluid, which is necessary for the maintenance and protection of spermatozoa [1].

The secret of the prostate gland mainly consists of prostaglandins, prostatic acid phosphatase, as well as other enzymes (for example hyaluronidase), fibrinolysin and fibrokinase, which contribute to the liquefaction of the seminal fluid and activating the movement of spermatozoa [1].

It also plays an important role in regulating the level of male hormones and can affect the functioning of the genitourinary system in general. There are barrier and secretory functions of the prostate gland. Therefore, maintaining prostate health is an important aspect of men's health. In case of chronic inflammation of the prostate gland, its functions are impaired. Features of the location of the prostate gland, direct connection with the urethra make it vulnerable to the development of infectious and different inflammatory diseases, in particular prostatitis [1].

Chronic diseases of the prostate gland (PG): chronic prostatitis (CP) and benign prostatic hyperplasia (BPH) - significantly affect the work efficiency, health and general psycho-emotional state of men [2].

Every year due to these diseases the population and states suffer significant economic damage, and prevalence rates are constantly increasing due to an increase in average life expectancy and the percentage of men in older age groups. Important factors in the development of inflammation of the prostate are blood circulation disorders in the organs of the small pelvis (congestion), sedentary work, irregular sex life or its absence, excessive cooling, stress, overload. According to current data, chronic inflammation of the gland as a result of microbial infection, the influence of polymorphic factors or hereditary predisposition often precedes or accompanies the development of BPH - a chronic progressive benign disease [2].

Against the background of age-related imbalance of sex hormones, prostatic glandular-stromal hyperplasia develops, accompanied by symptoms of the Lower Urinary Tract (LUTS) [2]. To date, there are no large-scale epidemiological studies of the internal population that would be similar to foreign ones. The etiology of BPH is multifactorial, and the development of the disease directly correlates with age, the level of prostate-specific antigen (PSA) and the volume of prostate [2].

Benign prostate hyperplasia is a benign disease characterized by an increase in the size of prostatic epithelial cells and stromal tissues, a decrease in the rate of urine flow, which causes disturbances, commonly known as LUTS [2].

Taking into account that the growth, differentiation and functioning of the PG are controlled by sex hormones, most theories of the pathogenesis of BPH contain questions of hormonal regulation. This is based both on the fact of the presence of androgen receptors and estrogen receptors in this gland, and on the facts of the formation of these hormones in the basal and luminal cells of the PG [2].

Sex hormones such as testosterone (T), dihydrotestosterone (DHT), progesterone and estrogens have been studied in the most detail, although the role of each in the progression and development of BPH and their pathogenetic role in the "hormone / receptor" interaction, mutual regulation remains insufficiently understood [2, 3].

The main hormone which regulates the growth of the prostate gland is 5α-DHT, which is formed from T in the epithelial and stromal cells of the gland with the participation of the enzyme 5α-reductase [2]. It has been established that DHT carries out direct and indirect modulation of cell differentiation, proliferation and apoptosis of cells, induces glandular hyperplasia of the PG, while stromal hyperplasia is regulated by estrogens [2, 4].

The T metabolite is also considered to play a central role in the pathogenesis of BPH, based on the results of large-scale studies that have found a positive correlation between the presence of BPH/ LUTS and changes in the levels of endogenous sex steroid hormones, in particular T and estrogens.

Several studies have described inversely proportional relationship between serum T levels (total or bioavailable) and the degree of BPH or LUTS expression [2, 5], which correlates well with the state of age-related androgen deficiency and the frequency of PG disease [2]. This was the basis for attempts to use T for replacement therapy in order to prevent age-related changes in PG. However, the Proscar study found low T levels (<300 ng/dl) in 21,7% of older men only who also had BPH [2, 6]. Therefore, the idea of androgen replacement therapy was rejected due to fears of a possible increase in BPH and LUTS [2].

The importance of the problem of treating CP can be based on the knowledge of the fact that it is the third leading disease after cancer and it can take the development of BPH and has social significance for

many reasons [2]. Conservative therapy of prostatitis requires an integrated approach, namely the use of drugs of different types of action [2, 7].

So, recently the traditional ideas about the importance of vitamin D in providing calcium-phosphorus metabolism and bone mineral density have been supplemented with data on its role in the regulation of reproductive and sexual functions in men [8-10]. At the same time, it has been shown that in the presence of D-hypovitaminosis, disturbances in spermatogenesis occur, and also disturbance in the erectile and ejaculatory components of the copulatory cycle [8, 11]. The authors proved that erectile dysfunction in men with D-hypovitaminosis is associated with a decrease in the level of testosterone in the blood [8, 12].

Also, in our own studies at the clinic of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine) the features of changes in erectile function has been established and its depending on the levels of vitamin D in the blood and androgen status in 47 young and middle-aged men (23-59 years old). The research was conducted in the autumn-winter period of 2019-2020. According to the results of own observations, it has been proven that the content of 25(OH)D in the blood of middle-aged men, regardless of the presence or absence of type 2 diabetes, was significantly lower compared to the group of young men. It has been proven that the formation of erectile dysfunction in both young and middle-aged men is due to a decrease in testosterone levels in the blood and a decrease in the T/E2 (testosterone/estradiol) ratio [8]. So, it has been established that a predecessor of the development of hypotestosterone and androgen-estrogen balance disorders in men regardless of age, in particular, patients with type 2 diabetes, can be a decrease in the blood content of 25(OH)D [8].

According to the World Health Organization, more than one billion people have vitamin D deficiency. Vitamin D deficiency is also present (in 81.8% of cases) in Ukraine. It has been established that vitamin D is necessary for adequate production of steroid hormones and full-fledged spermatogenesis, but its deficiency causes the development of androgen deficiency and pathospermia, which generally leads to a decrease in fertility. Also it has been reported that vitamin D receptor has an expression in cells of reproductive organs such as testes (Sertoli cells, seminiferous tubules, spermatogonial stem cells, etc.), epididymis, seminal vesicles (SV), prostate (PG), and even spermatozoa [13]. It indicates the necessity of vitamin D for adequate production of steroid hormones, and its deficiency can have a negative impact on the reproductive function of men [13].

In direction testosterone is a regulator of vitamin D receptor activity in the testicles. Vitamin D treatment led to an increase in the level of male sex hormones in the blood serum of patients with D-hypovitaminosis [13].

In addition, application of vitamin D in men with idiopathic oligoasthenozoospermia for three months, even without taking into account its concentration in the blood during treatment, improved sperm motility [13].

This indicates that the use of vitamin D for the treatment of reproductive disorders in men with pathology of the genital and prostate glands is possible both with and without D-hypovitaminosis.

Well known that only experimental arguments of vitamin D prescribing in pathology models simulating the most common variants of infertility can confirm these assumptions. These pathologies include chronic inflammatory processes in PG and SV, because subfertility in men with prostatitis remains one of the main causes of infertile marriages.

According to our observations at the laboratory of reproductive endocrinology of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine), experimental data about changes in the hormone synthetic function of the testicles during modeling of prostatitis, as well as cholecalciferol (D3) together with drugs which protect prostate gland have been presented. Thus 36 sexually active rats were administered vitamin D at a dose of 4000 IU (both monotherapy and in complex baseline regimens) to correct sex hormone levels and fructose concentrations in male rats with experimental abacterial prostatitis induced by cryotraumatization of the ventral part of the prostate gland. In this study, as in our previous ones, it was shown that modeling experimental prostate pathology by prostate cryotrauma leads to hypotestosteronemia and a decrease in serum testosterone/estradiol ratio in male rats. The concentration of fructose decreases almost 3 times in the seminal vesicles of animals with experimental prostatitis [13, 14]. The use of Prostatilenum* as monotherapy or in combination with vitamin D3 for the experimental treatment of prostatitis regardless of the methods of administration led to the normalization of testosterone levels (increased testosterone concentration in blood serum) and fructose content in the testicles but did not affect the concentration of estradiol. Independent use of vitamin D per os in conditions of experimental prostatitis did not lead to regeneration of testosterone secretion, but increased its effect on seminal vesicles. Prostatilenum* (Biopharma, Ukraine) is a biogenic preparation with prostate-protective action. This procedure is indicated by an increase in the mass of seminal vesicles and the concentration of fructose in them [13]. Therefore, the

introduction of complex treatment regimens of vitamin D with Prostatilenum* is advisable, because it positively affects the androgen saturation of the body, increases the concentration of fructose in the seminal vesicles, which can contribute to spermatogenesis and fertility [13].

This indicates an increase in the mass of seminal vesicles and the concentration of fructose in them [13].

Recently, the number of patients with benign prostatic hyperplasia (BPH) has been increasing. It was supposed earlier that BPH is observed in an average of 80% of men after the age of 60 [15]. Due to the rapid aging of the population, dynamic steps of life, stress and the effects of harmful environmental factors, BPH has become an important health problem worldwide. It is supposed that under such conditions, the number of men under the age of 50 who will have this disease increases [15], because such conditions cause a decrease in the secretion of androgens in men, metabolic disorders and dyshormonal conditions, which are now observed more often in the stressful existence of society than before. It is well known sexual function is very sensitive to harmful factors, under their influence both reproductive and copulatory components of male health change. Prolonged stress can cause hypofertility even infertility and sexual disorders. One of the main suppressing factors of spermatogenesis due to the stress is the occurrence of a number of hormonal changes – a decrease in the circulating level of testosterone, follicle-stimulating and luteinizing hormones with an increase in the concentration of corticosteroids, prolactin, and predominance the content of estrogens over androgens [16].

It is known that lifestyle factors, which are currently complicated by external influences, have a specific weight in the development of BPH [17]. Prevention and treatment of BPH is not only a medical, but also a serious social problem. Today, based on the results of research into the pathogenesis of the hyperplastic process in the gland and the mechanism of action of drugs, not only surgical, but also therapeutic treatment of BPH has taken an important place among other methods of its rehabilitation [18].

The pathogenesis of BPH is associated with regulatory disturbances in the hypothalamic-pituitary system and a change in the intensity of regulatory signals sent to the reproductive organs. The central pathogenetic links in the development of this pathology include a decrease in the efficiency of the regulation of hypothalamus functions, which is carried out according to the principle of feedback, the change in the sensitivity of pituitary cells to the releasing hormones of the hypothalamus and an imbalance between the production of estrogens and androgens. At the organ level the development of BPH is caused by an increasing in the activity of the enzyme 5-alpha-reductase which promotes the conversion of testosterone into dihydrotestosterone, an increasing in the synthesis of tissue growth factors and an increase in the expression of androgenic and alpha-1-adrenoceptors [2]. Among the adenohypophyseal hormones in addition to follicle-stimulating and luteinizing the development of BPH is greatly influenced by prolactin, the hypersecretion of which is considered to be a very significant cause of age-related hyperplastic processes in the prostate gland.

Prolactin stimulates proliferation and acts as an androgen-dependent suppressor of prostatic epithelial apoptosis, leading to prostatic hyperplasia. By the way, the increase in the level of prolactin under conditions of stress and its important etiopathogenetic role in reducing the reproductive capacity of the body are are universally accepted [19]. The experimental administration of dopamine receptor blockers, namely sulpiride, in BPH modeling, for a long time contributes to an increase in the level of prolactin and a decrease in the release of gonadotropic hormones [14, 20].

This model is widely used in experiments to study the prostatotropic activity of BPH drugs [21]. The sulpiride model which is characterized by the development of an imbalance of sex hormones and an inflammatory process in the body of rats [22] provoke the development of BPH is associated with a violation of testosterone synthesis in the testicles due to insufficient function of the PG, an increase in the content of prolactin and estradiol which then provokes proliferative changes in the organ which we have observed in 64 male rats during our the experiment at the laboratory of reproductive endocrinology of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine) [22].

With prolonged administration of sulpiride, whose neuroleptic properties are associated with antidopaminergic action, induces hypersecretion of prolactin, which leads to stimulation of the proliferation of the glandular epithelium of the PG. The pathogenesis of acinar hyperplasia is related to an increase in the activity of 5-alpha-reductase and an increase in the sensitivity of epithelial cells; in 50% of cases, the pathology develops against the background of chronic prostatitis and reduced sensitivity to androgens [22]. Considering the fact that the growth, differentiation, and functioning of PG is controlled by sex hormones, most theories of the pathogenesis of BPH pay attention to hormonal regulation also. This is based both on the presence of androgen receptors (AR) and estrogen receptors (ER) and on the formation of these hormones in the basal and luminal PG cells. The main hormone regulating gland growth is 5α-dihydrotestosterone

(5α-DHT), which is formed from testosterone (T) in epithelial and stromal cells [22].

BPH may occur due to their excessive growth in these cells of the epithelium and stroma of the gland. Espinosa G (2013) writes that the prevalence of vitamin D deficiency in the «male urological population» may indicate an association between BPH and vitamin D. Vitamin D has an inhibitory effect on the RhoA/ROCK pathway together with cyclooxygenase-2 expression and prostaglandin E2 production in stromal cells of BPH. It has been shown increasing of dietary vitamin D intake with food and nutritional supplements correlate with a decrease in the prevalence of BPH, and vitamin D analogues reduce prostate volume in patients with this pathology. Preclinical studies have shown that vitamin D not only reduces prostate cell proliferation in BPH when induced by well known growth-promoting molecules such as IL-8, Des(1-3) IGF-1, testosterone and dihydrotestosterone [15].

Among all these studies, there were no side effects or negative effects with increased vitamin D intake (Espinosa G., 2013). Against the background of BPH, reproductive disorders have been diagnosed, such as sexual disorders, spermatopathy, hypofertility, which may be caused by increased production of reactive oxygen radicals during inflammation due to prostatitis [23].

Usually BPH therapy includes a complex of measures such as the use of α1-blockers (in particular, doxosazin, tamsulosin, silodosin), 5α-reductase inhibitors, phosphodiesterase type 5 inhibitors, anticholinergic and pronorepine drugs (3β). However, when prescribing such therapy one should take into account a large number of side effects associated with the consequences of prolonged dilation of small vessels such as a decrease in sperm production, gynecomastia (breast enlargement) and other [22].

Based on the recommendations of international urological associations for the conservative therapy of BPH, the following pharmacotherapeutic groups are selected: α1-adrenergic agents, 5α-reductase inhibitors, anticholinergic drugs, antihormonal drugs, NSAIDs. Systemic drugs may have a significant number of side effects. So, for example: the effect of 5α-reductase inhibitors is negative in damage from the side of the reproductive system. This is unacceptable, because according to statistics, BPH occurs in men of reproductive age, reduces their sexual activity, impairs fertility, which significantly affects the quality of life. However, taking into account the positive results of the treatment of pathology, this group of pharmaceuticals continues to be chosen by many doctors as an alternative to surgical intervention [23].

More often the search of scientists is focusing on the search for substances for the treatment of BPH among herbal medicines as an adequate alternative, devoid of the main disadvantages of systemic prostate protectors [14]. According to Zaijchenko G.V. (2018) herbal drugs have a wider therapeutic range, are safer than other groups of drugs, often acting as the drugs of choice for men with BPH under 55 years of age. However, their lack of knowledge does not allow them to be considered more effective than α1-agonists and 5α-reductase inhibitors. It is perspective to use combined drugs which contains several active ingredients with different mechanisms of action and using drugs of different pharmacological groups. So, recently a pharmaceutical composition has been created which includes indole-3-carbinol and meloxicam, capable of inhibiting the biosynthesis of prostaglandins - inflammatory mediators and preventing carcinogenesis in the prostate gland. Currently, there are several drugs and dietary supplements containing indole-3-carbinol (Indigal, Prostadoz, Saluprost, Indole forte, etc.) in combination with vitamins, epigallocatechin-3-gallate and the most active green tea catechin [2, 24].

This motivates to look for new ways of prevention and treatment of BPH. The data accumulated in recent decades indicate that traditional methods of treating BPH disease are not very effective and the use of antibiotics and alpha-blockers in chronic nonspecific prostatitis does not change the so-called Chronic Prostatitis Symptom Index (National Institutes of Health, USA), although a positive effect has been found of muscle relaxant therapy [25]. They also note a significant placebo effect and suppose that it is combination therapy with the introduction of anti-inflammatory and immunomodulatory agents that increases the effectiveness of therapy [26]. IL-1 and C-reactive protein are objective criteria for the severity of chronic inflammation, the levels of which can be used to monitor the effectiveness of therapy [27].

There are drugs based on natural compounds in particular from plant materials among the drugs with anti-inflammatory and immunomodulatory effects [28].

Serenoa repens fruit extract (Prostamol® Uno) is widely used for the treatment of chronic prostatitis and the prevention of prostate adenoma [29], although the data obtained are contradictory. A drug composition containing an extract of broccoli and nettle has been created, and its effect on the inhibition of BPH has been shown [30].

As noted above, the prevention and treatment of PG diseases has not only medical, but also social significance. Prostatogenic decrease in fertility can have different causes, most often associated with a violation of the

structure and function of the prostate gland by itself. One of the urgent problems of today is the study of the effect of the D-hormone on the body [31], while in men its action is closely associated with the pathogenesis of androgen deficiency and hypofertility [32].

There is evidence that the level of vitamin D describes the qualitative and quantitative characteristics of the ejaculate in young people [33], including the motility and morphology of spermatozoa [34], is important in the maturation of spermatozoa.

A relationship has been found between low levels of vitamin D and a decrease in the number of motile and morphologically normal spermatozoa [35]. Vitamin D deficiency in animals leads to disruption of the maturation of the vas deferens, a decrease in testicular mass and sperm concentration [36]. Experimental studies have shown that vitamin D saturation leads to a significant improvement in spermatogenesis in experimental reproductive disorders [37-38].

Data reported in the literature about the use of vitamin D in males demonstrate wide variability in design, methodology, patient population, reference values, and routes of administration for both vitamin D itself and its metabolites, and require further research. Vitamin D belongs to the group of fat-soluble secosteroids. A secosteroid is a molecule that is very similar to steroids, but with a torn-apart of steroid ring. Vitamin D occurs in nature in several forms, but only two forms (D2 and D3) are important to the human body, which differ chemically in their side chains. These structural differences change their binding to the carrier protein, vitamin D-binding protein and their metabolism, but in general, the biological activity of these active derivatives is similar [39].

Data from the literature indicate that vitamin D has an inhibitory effect on the production of prostaglandin E2 in the stromal cells of BPH. An increase in dietary and supplemental vitamin D intake was correlated with a decrease in the prevalence of BPH. It has been shown by Espinosa G. (2013) vitamin D analogues can reduce prostate volume in patients with BPH. Preclinical trials have shown that vitamin D reduces BPH cell proliferation through induction by known growth-promoting molecules such as IL-8, Des(1-3) IGF-1, testosterone, and dihydrotestosterone. Among all studies, there were no side effects or adverse effects with increased vitamin D intake [15]. The effect of vitamin D on prostate volume and BPH has shown perspective results, therefore, it is proposed to conduct further studies on the role of vitamin D in the formation of BPH and reproductive disorders, their prevention and treatment. The use of vitamin D as monotherapy or in the form of pharmaceutical compositions and its inclusion in basic treatment regimens can increase the effectiveness of the prevention and correction of reproductopathies in the presence of or due to BPH and suggests the possibility of restoring the generative potential of individuals with BPH, both with and without D-hypovitaminosis [40].

Summing up this report, the following conclusion can be exposed leaving some questions open for research:

CONCLUSIONS

1. Considering the fact that one of the main reasons for the impairment of male fertility is the disease of the reproductive system, in particular, BPH, which is a common pathology of the male reproductive system, however, the reconstruction of male health in this pathology is not effective enough, this determines the urgency of developing new drugs for the correction of BPH and consequences for the reproductive system.
2. Particular attention needs to be given the answer to the question if the introduction of cholecalciferol (D3), which is the most active of the metabolites of this vitamin and is often used in the clinic, has a negative effect on the gonads and spermatogenesis of intact individuals during long-term use, since vitamin D therapy is used in reproductive diseases such as with vitamin D deficiency and without it

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REVIEW ARTICLE

CONTENTS

Aggressive parenting: social, medical and legal aspects

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ABSTRACT

Aim: To examine the impacts of aggressive parenting on physical, mental and emotional development; outcomes for society; possible ways of prevention of children' rights or health violation and responsibility of parents to optimize well-being of children.

Materials and Methods: The analysis of scientific data has been conducted on the basis of PubMed, Scopus and Web of Science databases in order to collect the existed results of researches about social and medical aspects of impact of aggressive parenting. The formal-legal method was used to interpret the provisions of legislation regarding the protection of personal non-property rights and responsibilities of parents and children.

Conclusions: Aggressive parenting affects children of all ages and is associated with chronic stress and long-term negative impacts on physical development, cognitive and behavioral dysfunction, socioemotional difficulties, social and psychological dysfunction in adulthood. Aggressive parenting triggers a child' aggressive behavior which is considered as a predictor of adult's criminality. From a legal standpoint, aggressive parenting is a form of violation of the responsibility of parents to educate a child, which is an element of family legal relations regulated by the norms of the family law institution known as «Personal non-property rights and responsibilities of parents and children". The definition of aggressive parenting has been defined with its legal features and characteristics. Effective prevention methods should be directed to predict possible further parental violence, intervention programs to reduce outcomes of aggressive parenting and to improve the ways of responsibility in procedural and material aspects of law.

KEY WORDS: Harsh parenting, children' health outcomes, ways of prevention, legal responsibility, Family law

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INTRODUCTION

A parenthood is a key mission, significant condition and considerable social and psychological function of humans. The style of parenthood is the base for development of individual's qualities, influences the adaptation to surrounding conditions and eventually affects the society as a whole [1].

Mindful parenthood is the one of the complicated aspects of Psychology and Pedagogy, moreover Medicine and Jurisprudence due to an increase in an aggressive style of bringing up with numerous outcomes [2].

A term "parenting" has many varieties of definitions aimed to developing the complete individual in all the aspects of human being and refers to a process of raising children providing them with protection in order to promote well-being such as support of physical, intelligential, emotional, spiritual and social development and achieved by certain parental style [3]. A parental style, meanwhile, is considered with characteristic attitude of parents toward the children. It is important to note that many factors can affect style of parenting like cultural, religious, social, political, economic, etc. [4]. Moreover, numerous studies have shown the psychiatric effects of the military deployments on adults, families and children [5-8].

Child development is influenced by different factors in both positive or negative ways, in the same time, the mental health of adults largely depends on family environment at which they have been as children [9].

Aggressive parenting is considered as style using threats or different kinds of punishments such as psychological or physical to keep a child under control or pressure to obey. However, the standardized definition of aggressive parenting doesn't exist and most of interpretations are focused on physical aggression which refers to actions with intention of causing physical pain or injury.

Regarding physical aggression, it is associated with wide range of aggressive behavior such as kicking, spanking, hitting with a fist, slapping on the face, beating up, burning or scalding, grabbing or choking around the neck, threatening with a knife or gun, pinching,

or shaking children, thus including everything from severe physical injuries to culturally acceptable kinds of punishments [10].

Nevertheless, psychological aggression is considered as a persisting pattern of behavior making children to feel that they are unloved, worthless, unwanted, and is the most common form of aggressive parenting behavior including all kinds of psychological control such as guilt induction, yelling, cursing, threatening or name calling and other, used to pressure and to manipulate behavior and thoughts of children [11].

Moreover, researchers have found that psychological aggressive parenting, rather than physical, was a more powerful predictor of depression and self-esteem [10].

In the legal context, we deal with one of the Institutions of Family Law «Personal non-property rights and responsibilities of parents and children». These are the rights that a person cannot refuse and the observance of which can be demanded from everyone [12]. According to art. 150 «Parental Responsibilities in respect of the Child's Education and Development» of the Family code of Ukraine, the parents shall educate the child in the spirit of respect for the rights and freedoms of the others, love to his/her family and relatives, people and Motherland. The parents shall have the duty to care of the child's health, his/her physical, spiritual and moral development. The parents shall pay respect for the child, ensure that the child obtains full general secondary education and shall prepare him/her to his/her own life [13, 14]. From this point of view, aggressive parenting can be considered as a non-fulfilment or improper fulfillment of the parental responsibility of the child's education.

Taking in account the current martial law in Ukraine, as an additional possible factor initiating aggressive parenting, it is impotent and relevant to be aware of the seriousness of Russia-Ukrainian war outcomes.

AIM

The aim of the study was to examine the impacts of aggressive parenting on three aspects of personality development such as physical, mental and emotional; outcomes for society; possible ways of primary, secondary and tertiary prevention of children' rights or health violation and responsibility of parents to optimize well-being of children, and consequently, well-being of future adults or to provide perspectives for healthy nation; issues of legal responsibility for aggressive parenting.

MATERIALS AND METHODS

This article has been written using a range of scientific methods that have facilitated an objective and comprehensive examination of the issues covered by the research purpose. The analysis of scientific data has been conducted on the basis of PubMed, Scopus and Web of Science databases in order to collect the existed results of researches about social and medical aspects of impact of aggressive parenting. Synergistic method provides the collaborative interdisciplinary research. Bringing together experts from medicine and legal fields, let us combine unique perspectives, methodologies, and expertise to tackle multifaceted problems of aggressive parenting and generate integrative approach to push the boundaries of knowledge. The formal-legal method was used to interpret the provisions of legislation regarding the protection of personal non-property rights and responsibilities of parents and children. Logical methods of analysis and synthesis have allowed for the derivation of comprehensive knowledge about the essential characteristics of aggressive parenting in social, medical and legal aspects, particularly, comparative legal to compare legal regulation of subject in different jurisdictions, statistical to collect and process the necessary data and other [15].

REVIEW AND DISCUSSION

Numerous studies showed a relationship between childhood environment and long-term neurobiological and psychological development, where environmental factors may produce the risk of different psychiatric disorders development, disorders of physical development, also can affect functions of visceral organs resulting in cardiovascular disorders, adult obesity and diabetes, thus early-life environment impacting the adulthood [16].

CHARACTERIZING PARENTAL STYLES

Currently the following parenting styles are used in psychology, including authoritative, authoritarian, permissive and neglectful or uninvolved, based on two aspects of parents' behavior – demanding and responsive.

The results of researches have shown that authoritative style promotes positive well-being of adolescents, they are less likely to be with externalizing disorders, also less involved in drug abuse or criminal activity [17]. Additionally, it has been revealed that children with authoritative style of parenting have lower levels of depression and anxiety and with higher level of self-estimation and life-satisfaction [18].

Authoritarian style is associated with verbal abuse and psychological control [19]. Adolescents with authoritarian style have been shown to have negative

psychological effects, poor social skills, reducing self-esteem, psychological flexibility and maturity, moreover can lead to depression and mania [20].

Adolescents with permissive style frequently show substance use, low self-esteem, school misconduct, low extrinsic motivational orientation and less positive orientation to school [21].

An uninvolved style is considered to have the most negative effect on personality development [22]. Adolescents have been shown to have trouble controlling emotions, academic challenges, problems with maintenance of social relationship [23]. Also, researchers have found the association between uninvolved parenting style and delinquent acts such as vandalism, theft, attack and rape, more frequently they are found to drink alcohol, smoke, drug use, have high risk of depressive symptoms [21].

As it is seen from the data of researches, the parenting style has a great impact on the development of anxiety and depression which is characterized by aggressive behavior and violence [18, 23, 24].

In turn, anxiety is connected to fear and oriented to cognitive, affective, physiological and behavioral responses for the preparation to anticipate the threatening [25]. It is important to mention that the manifestations of anxiety and fear in the body are the same [26]. Some researchers revealed the evidence and strong correlation between aggression and anxiety based on neuroendocrine and neurochemical mechanisms [27]. Individuals with anxiety disorders often show intensive anger and aggression, in same time, they are characterized by social phobia associated with violent behavior [28].

The uninvolved and authoritarian styles of parenting are positively related to the development of depression symptoms, as it has been shown in research, conducted by Brittany N. Hearne (2015) [29]. Additionally, author concluded that parental style affects educational achievements and educational progress though mental health.

IMPACT OF STRESS ON COGNITIVE FUNCTIONS

Parental aggression is also linked to stress, at same time, stress is a most significant cause of depression. Stress initiates release of adrenocorticotropic hormone, stimulated by corticotrophin-releasing hormone from hypothalamus, that results in secretion of glucocorticoids (GC) by adrenal cortex, providing elevated concentration in blood and cerebrospinal fluid [30]. Additionally, chronic stress maintains elevated basal concentration of GC [31]. Normally, negative feedback mechanism suppresses secretion of corticotrophin-releasing hormone via GC receptors in the hippocampus thus normalizing concentration of GC, however in case of depressive disorder the lack of negative feedback leads to the continuation of elevated GC level [30]. Chronic stress with elevated basal level of GC induces atrophy of hippocampal neurons with respective alteration of functions such as learning and memory [32].

Among widespread systemic effects of GC on visceral organs and stress-adaptation they are also involved in learning and memory, cognitive functions and reward-related behaviors [33].

Glucocorticoids change synthesis and metabolism of neurotransmitters and neuromodulators, such as serotonin, dopamine, glutamate and GABA, altering the physiological level of their receptors [34]. In the other hand, the listed above substances play a crucial role in the pathophysiology of depression.

Deficiency of serotonin and impaired receptors lead to depression, anxiety and other mental health disorders, moreover, researchers revealed that social isolation and hypercortisolemia are the causes of serotonin receptors alteration [35].

There is evidence that stress with elevated basal GCs level during adolescence can affect brain development leading to maladaptive changes later in life impacting behavior and stress responsiveness. Particularly, stress hormones can change dopamine neurotransmission thus alter dopamine-mediated cognitive function and behavior during adolescence. It has been revealed that chronic stress induces dopamine-related changes in the prefrontal cortex (PFC), namely decrease basal dopamine level, expression of receptors and binding, leading to abnormal behavior like increased aggression, anxiety-like behavior and decrease social interaction. Obtained results allowed to suggest that chronic stress during adolescence may affect dopaminergic circuits resulting in long-term molecular and behavioral maladaptation in adulthood. Adolescence is a period of development of the body and brain, any trigger, particularly stress, affecting brain maturation, lead to disturbance of adaptive behavior, which normally facilitates adolescent's independent development, tolerance to psychosocial stress, inhibitory control, long-term planning and abstract problem solving which are necessary to handle with variety of cognitive and social requests during adulthood. However, abnormal brain maturation at adolescence may play a critical role in mental illness such as schizophrenia, bipolar illness, depression and drug abuse [36].

Another important and the major excitatory neurotransmitter of the healthy brain is glutamate, moreover, most neurons express at least one type of recep-

tors for glutamate. Glutamate plays an important role in variety of neuroplasticity mechanisms, that is crucial in all areas where neuroplasticity is essential for adaptation to environmental stressors such as cognition, learning, memory and mood. At the same time, chronic stress impairs glutamate system and reduces neuroplasticity. It was revealed that in the hippocampus chronic stress increases glutamate release, affecting long-term potentiation, causing atrophy of apical dendrites thus disturbing learning and memory. In contrast to hippocampus, in PFC and amygdala chronic stress decreases glutamate release resulting in impaired attention and anxiety. Researchers have proposed that the listed outcomes are due to neuroinflammation, affecting both intracellular and extracellular signaling pathways [37].

Regarding GABA, which is the main inhibitory neurotransmitter in brain circuits, and necessary for keeping the balance between neuronal excitation and inhibition processes [38]. Additionally, GABA is well-known regulator of physiological response to stress via regulation of hypothalamo-pituitary-adrenal axis function [39]. Numerous studies indicate the direct relationship between stress and GABA-modulation in the amygdala – a part of brain responsible for emotional aspects of learning and behavior.

There is evidence that early-life stress produces alteration in GABA-receptors expression inducing long-term changes in behavior and stress response thus providing molecular basis for the effects of early-life stress on adulthood anxiety [40].

THE IMPACT OF AGGRESSIVE PARENTING ON PHYSICAL DEVELOPMENT OF PERSONALITY

In a healthy organism a physical development is mainly provided by environmental, dietary, socioeconomic, behavioral, metabolic, biochemical, and mainly genetical and hormonal factors. In our review we discussed the hormonal aspect of physical development and its alterations caused by aggression. The following substances are vitally important to provide physical development such as growth hormone, insulin-like growth factor 1, sex steroids, and thyroid hormone.

Growth hormone is crucial for children' physical development with progressive rise of its level during childhood and peak that occurs in puberty. Meanwhile, infants, children and adolescents represent the period of aging with increased vulnerability to environmental stressors .

Existing results of studies show the negative effects of chronic stress on growth, where high cortisol suppresses growth hormone-insulin-like growth factor 1, hypothalamic-pituitary-gonadal and thyroid axes leading to visceral obesity, a decrease in lean mass, inhibition of osteoblasts activity with high risk of osteoporosis and induction of insulin resistance. Additionally, during sensitive growth periods, chronic stress can affect body morphology, increasing risk of short stature and obesity. It also has been found that neglectful parenting style is associated with an increased risk of obesity in childhood, adolescence and adulthood, long-term emotional abuse leads to growth failure.

IMPACT OF AGGRESSIVE PARENTING ON MENTAL DEVELOPMENT

There is numerous scientific evidence that positive parenting style in childhood has benefits for mental health and preventing adolescents psychiatric and behavioral problems. Relatively to mental health and development it has been revealed that positive parenting is widely protective against internalizing and externalizing behavioral problems, in contrast, aggressive style or harsh discipline including screaming, cursing, threatening and physical punishment, is associated with higher level of the symptoms of internalizing and externalizing behavioral problems, and is considered to be detrimental to children's socioemotional development. Whereas, internalizing behavioral problems are associated with own self focus and expressed by withdrawal, anxiety, depression and emotional problems; externalizing behavioral problems occur in interaction with the social environment result in aggression, impulsivity, deviance and hyperactivity. Moreover, in respect to sex differences, it has been also revealed that among girls positive parenting was associated with lower expression of physical, social aggression, and suicides. Further, other results of researches have shown that parents-adolescents' conflicts are related to higher adolescents' anxiety, depression, aggression, lower school satisfaction and lower self-esteem; at same time, positive parenting, which is expressed in parent support, education support and parent-child future orientation, is associated with less depression and higher self-esteem, future optimism and school satisfaction.

AGGRESSIVE PARENTING INITIATES A DEVELOPMENT OF CHILD' AGGRESSIVE BEHAVIOR

It is known that child aggressive behavior is one of the best predictors of adult's criminality. The results of conducted studies showed that aggressive children are less intelligent, less popular, have parents who use different physical punishments, and less likely to express guilt.

Moreover, aggressive children express more family disharmony and are most at the risk for arrest. Besides, the level of aggression at age eight is considered as the best predictor of criminal events over the next 22 years, thus prevention methods have to be targeted on risk factors of early aggression development. The severity of aggression, emotional dysregulation and social isolation is a potent and direct predictor of violent crime; thus, adolescents' socialization plays a special role in predicting nonviolent and violent crime.

Existing results of conducted researches have shown that the military personnel deployed in war are at a high risk of mental health disorders, especially posttraumatic stress disorder, with following affection of family members, particularly children.

As psychological difficulties in adults may affect parenting capabilities so that posttraumatic stress disorder can cause negative changes to an individual's behavior such as anger and reactivity and social withdrawal resulting in psychological, social and emotional difficulties in children. Moreover, parental posttraumatic stress disorder is associated with increased level of parental stress, expressed in detrimental effects to parenting satisfaction, parent-child relationship and acceptance of negative parental practices. Parents with posttraumatic stress disorder have an effect on internalizing and externalizing symptoms of children, including depression, social emotional adjustment, increased anxiety in early childhood.

Therefore, numerous studies show that children who grow up in environment with aggressive parenting may be more prone to be engaged in behaviors that can lead to criminal activity and break the law. In turn, the prevention of aggressive parenting will result in a decrease in juvenile delinquency as well as the overall crime rate in society.

THE WAYS OF PREVENTION

In prevention of child abuse, it is crucial to identify the probability of aggressive parenting style use, the term known as child abuse potential and linked to abusive physical discipline and harsh, authoritarian parenting. Aggressive parenting and child abuse potential collectively termed as parent-child aggression risk. Researchers attempted to identify the processes involved in increasing the risk adapting the Social Information Processing theory, i.e., a third theory of conduct problems which is focused on processing of information in the social situations. The evaluation controlled for parents' level of personal vulnerabilities such as psychopathology, substance use, domestic violence and resiliencies like social support, partner satisfaction and coping in order to define the predictive value of Social Information Processing theory.

The primary prevention has to be aimed at reducing risks or threats to health thus it is crucial to assess the tendency to aggressive parenting prenatally, for example, after marriage registration, or while planning for pregnancy, such comprehensive approach gives opportunity to detect specific problematic areas for family. The correction of possible parents' harsh behavior may include enriching the emphatic skills, improvement of emotion regulation skills, frustration tolerance. The improvement and correction of parental skills could be performed individually for particular family or universally, through a more public health by widely spread programs of aggressive behavior correction preparing the adults to mindful parenthood.

Secondary prevention. As secondary prevention underlines early detection of pathological changes so that it has to be done in different forms of screenings in order to reveal the degree of depression, anxiety, poor work performance, inability to learn, substance abuse, quality of life and worry. In achievement of this goal, it is crucial to assess the psychological flexibility which refers to ability of individual to react properly to different circumstances and emotional demands in order to achieve goals and related to self-control, self-regulation, and emotion regulation. Thus, psychological flexibility measures adaptation to fluctuating situational demands, ability to reconfigure mental resources and to balance competing desires, needs, and life domains. For purpose to assess the psychological flexibility the Acceptance and Action Questionnaire can be used which has been adapted to specific population and psychopathologies including psychic symptoms (Voice Acceptance and Action Scale), social anxiety (Social Anxiety – Acceptance and Action Questionnaire), Avoidance and Fusion Questionnaire for Youth and Child and Adolescent Mindfulness. The analysis of the associations between psychological flexibility, psychological and social impacts allowed for researchers to reveal that low psychological flexibility is linked with psychopathologies and is greatly influenced by parenting style.

Tertiary prevention. Tertiary prevention aims to reduce the effects of the aggressive parenting and can be directed to both children and parents. Existing results of studies reported that some coping strategies (processes of executing a cognitive response to threat), such as avoiding contact with aggressor or disclosing violence to confidant, make victims feel better [11]. However, complete assessment of family members with individual approach for both parents and children, who facing the violence is a crucial. In this step

it is important to examine children' vulnerability, the degree of psychological and physiological changes, and stress tolerance. Interventions directed to parents have to be based on improvement of parental practice and sensitivity, learning effective parental skills with recommended programs by social services and to adopt an authoritative style of parenting which is considered as the best style, warm and responsive. Regarding children, the respite care might be helpful in order to improve cognition, self-esteem and social skills; group therapy is also proved useful and motivating for victims of parental violence.

The ways of responsibility.

As we mentioned earlier, in the legal context, aggressive parenting can be considered as a non-fulfilment or improper fulfillment of the parental responsibility of the child's education.

The current family legislation of Ukraine defines the education of a child as the responsibility of their parents, it`s according with the fundamental principles of international conventions. According to par.1 art. 18 of the United Nations Convention on the Rights of the Child, participating states make every effort to ensure the recognition of the principle of shared and equal responsibility of both parents for the education and development of the child. Parents or legal guardians bear the primary responsibility for the education and development of the child. The best interests of the child are the subject of their primary care.

In the theory of family law, the parental responsibility of the education of a child is defined as the measure of proper behavior, manifested through personal influence on the child, comparing one's actions with the requirements of pedagogy, moral norms, and morality, as well as the law to raise them in a spirit of loyalty to the homeland.

The legal definition that approximates the concept of aggressive parenting is the definition of "cruel treatment of a child" which encompasses any forms of physical, psychological, sexual, or economic violence against a child, including domestic violence, as well as any illegal actions concerning the child, such as recruitment, transportation, concealment, transfer, or receipt of a child, committed for the purpose of exploitation, using deception, blackmail, or the vulnerable state of the child. This definition is broader than aggressive parenting phenomenon as it: (1) encompasses actions that do not have the characteristics of parenting and; (2) applies not only to parents or other authorized persons responsible for the parenting, but also to any other individuals resorting to cruel treatment of the child.

Considering all, from a legal point of view, aggressive parenting can be regarded as a non-fulfilment or improper fulfilment of the responsibility of child education, manifested in a negative influence on the child, which contradicts the principles of morality, law, and the best interests of the child.

Legal responsibility for aggressive parenting should occur depending on the nature of the actions of the subject of parenting. According to paragraph 4 of Art. 155 of the Family code of Ukraine, evasion of performance of parental responsibilities constitutes the ground for bringing parents to responsibility prescribed by law. In particular, the court may deprive the mother or the father of parental rights if he/she: (1) evades parental responsibilities to educate the child; (2) behaves with child violently; (3) use different ways of exploitation, involves him/her in begging and vagrancy (par. 2, 3, 5 art. 164 of the Family code of Ukraine).

If aggressive parenting has signs of an administrative offense, then the parent has to be brought to administrative responsibility in order to Art. 184 «Non-fulfilment by parents or persons replacing them of their responsibilities regarding to the education of the child» of the Code of Ukraine on Administrative Offenses.

In some cases, aggressive parenting can take the form of a criminal offense. For example, the Art. 304 «Engaging minors in criminal activity» of the Criminal Code of Ukraine provides criminal responsibility for engaging minors in criminal activity, drinking alcohol, begging, or gambling.

However, the legal regulation of responsibility for aggressive parenting can be enhanced. Such enhancement should encompass both procedural and material aspects of responsibility.

The material aspect is associated with the establishment, at the legislative level, of new additional corpus delicti of administrative and criminal offenses, which should take into account specific forms of aggressive parenting and the corresponding negative consequences that have occurred for the child and social relations.

The procedural aspect can be associated with a broader and mandatory involvement of relevant specialists, such as psychologists, educators, doctors, and child protection workers, in the process of considering civil, administrative, or criminal cases. Involving these experts will contribute to the effective protection of the rights and legitimate interests of children who have experienced aggressive parenting. Furthermore, it is deemed appropriate to establish courts for minors and juveniles in Ukraine.

International experience supports the existence of separate jurisdiction courts specializing in cases related to children and the concept of juvenile justice in Ukraine is in the process of implementation.

CONCLUSIONS

Analysis of scientific data allowed to conclude the following:

1. Among all parental styles the authoritative style promotes positive well-being of adolescents, with higher level of self-esteem and life-satisfaction and lower levels of depression and anxiety and. In contrast to authoritative, permissive style results in frequent substance use, low self-esteem, school misconduct, low extrinsic motivational orientation. An uninvolved style is also considered to have the negative effects on personality development such as trouble controlling emotions, academic challenges, problems with maintenance of social relationships, delinquent acts like vandalism, theft, attack and rape, more frequently they are found to drink alcohol, smoke, drug use, have high risk of depressive symptoms. Authoritarian style is associated with verbal abuse and psychological control, adolescents have poor social skills, low self-esteem, psychological flexibility and maturity, moreover this style can lead to depression and mania.
2. It has been determined that aggressive parenting, from a legal standpoint, is a form of violation of the responsibility of parents (or other authorized persons) to educate a child. This responsibility is an element of family legal relations regulated by the norms of the family law institution known as «Personal non-property rights and responsibilities of parents and children".
3. Early-life adversities caused by aggressive parenting are associated with chronic stress and long-term negative effects to physical development, cognitive and behavioral dysfunction, socioemotional difficulties, social and psychological dysfunction throughout the lifespan. In turn, elevated basal glucocorticoids level change synthesis and metabolism of serotonin, dopamine, glutamate and GABA, altering the physiological level of their receptors leading to depression, anxiety and other mental health disorders, abnormal behavior like increased aggression, decrease social interaction. Moreover, chronic stress during adolescence may result in long-term molecular and behavioral maladaptation in adulthood, additionally, abnormal brain maturation at adolescence may play a critical role in mental illness such as schizophrenia, bipolar illness, depression and drug abuse. High cortisol suppresses growth hormone-insulin-like growth factor 1, hypothalamic-pituitary-gonadal and thyroid axes leading to visceral obesity, a decrease in lean mass, inhibition of osteoblasts activity with high risk of osteoporosis and induction of insulin resistance. During sensitive growth periods, chronic stress can affect body morphology, increasing risk of short stature and obesity.
4. Aggressive style is associated with higher level of the symptoms of internalizing and externalizing behavioral problems, and is considered to be detrimental to children's socioemotional development. Aggressive parenting is a trigger of child' aggressive behavior which is one of the best predictors of adult's criminality. Aggressive children are less intelligent, less popular, and less likely to express guilt, express more family disharmony and are the most at the risk for arrest. The severity of aggression, emotional dysregulation and social isolation is a potent and direct predictor of violent crime. Military personnel deployed in war are at a high risk of mental health disorders, especially posttraumatic stress disorder, with following affection of family members, particularly children.
5. The definition of aggressive parenting has been formulated, defining its legal features and characteristics. Specifically, aggressive parenting should be understood as non-fulfilment or improper fulfilment of the responsibility of child education, manifested in a negative influence on the child, which contradicts the principles of morality, law, and the best interests of the child.
6. Aggressive parenting affects children of all ages. Prevention of aggressive parenting will result in a decrease in juvenile delinquency as well as the overall crime rate in society. Effective prevention methods should be directed to predict possible further parental violence, intervention programs to reduce outcomes of aggressive parenting and to improve the ways of responsibility in procedural and material aspects of law.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

The impact of mitochondrial dysfunction on the pathogenesis of atherosclerosis

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ABSTRACT

Aim: To determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis based on the analysis of research data and statistics from the MEDLINE, Scopus and Web of Science Core Collection electronic databases for 2007-2023.

Materials and Methods: A comprehensive review of literature sources from the MEDLINE, Scopus and Web of Science Core Collection electronic databases was conducted to critically analyse the data and determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis.

Conclusions: In this review, we have summarized the latest literature data on the association between mitochondrial dysfunction and the development of atherosclerosis. Mitochondria have been recognized as a novel therapeutic target in the development of atherosclerosis. However, the presence of current gaps in therapeutic strategies for mitochondrial dysfunction control still hinders clinical success in the prevention and treatment of atherosclerosis. Both antioxidants and gene therapy are appealing approaches to treating atherosclerosis. Nevertheless, further research is needed to determine the proper therapeutic strategy to reduce the impact of mitochondrial dysfunction on the progression of atherosclerosis.

KEY WORDS: atherosclerosis, oxidative stress, mitochondria, mitochondrial dysfunction, mitochondrial DNA

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INTRODUCTION

Atherosclerosis is a multifactorial disease associated with endothelial dysfunction and oxidative stress, which, along with accompanying cardiovascular diseases, remains the leading cause of mortality worldwide [1]. The prevalence of atherosclerosis increases with the ageing of the population. Coronary heart disease and stroke are among the dangerous and life-threatening consequences of atherosclerosis. Therefore, better understanding of the pathogenesis of this disease at early stages is crucial for the development of its effective treatment methods [2, 3].

A large number of clinical studies have clearly demonstrated that control of modifiable risk factors is insufficient to limit atherosclerotic vascular damage, which underlies most cardiovascular diseases [4,5]. The initial reference to the link between mitochondria and atherosclerosis can be traced back to 1970. However, in recent years, a significant body of evidence has emerged regarding the key role of mitochondrial dysfunction in the pathogenesis of atherosclerosis. Mitochondria are known to regulate the inflammatory response and oxidative stress, being the two crucial stages that, when dysfunctional, can modulate the initiation and progression of atherosclerosis [6].

Mitochondria play an important role in the vital aspects of cell functioning. They are involved in the regulation of apoptosis, cell cycle, cell development, reactive oxygen species (ROS) generation, cell signal transmission, as well as intracellular Ca^{2+}homeostasis [7]. However, the primary function of mitochondria is the generation of energy in the form of adenosine triphosphate (ATP), which covers approximately 95% of the cell energy demands. This function is vital, especially for energy-consuming cells such as neurons and cardiomyocytes. Therefore, mitochondrial dysfunction and damage to mitochondrial ultrastructure can have a significant impact on overall cellular function [8]. In addition, mitochondrial dysfunction plays a major role in myocardial ischemia, which is characterised by a decrease in mitochondrial metabolic enzymes, ATP content, the opening of the mitochondrial permeability transition pore, leading to the release of reactive oxygen species, and the absorption of Ca^{2+}, with the

subsequent development of apoptosis or necrosis of cardiomyocytes [9, 10].

The myocardium is one of the most energy-demanding organs in the human body, consuming from 6 to 30 kg of ATP per day in the mitochondria, often referred to as the power plant of cardiomyocytes [11]. Therefore, mitochondrial disorders are associated with a high frequency of cardiac impairments, primarily characterized by myocardial metabolic disturbances [7, 12].

It is known that in addition to nuclear DNA, mitochondria have their own genome called mitochondrial DNA (mtDNA) [7]. A cell contains hundreds of mitochondria, and each mitochondrion contains from five to ten copies of mtDNA. Human mtDNA is a double-stranded circular molecule that encodes 37 genes: 13 for the core subunits of the oxidative phosphorylation system, 2 for rRNA, and 22 for tRNA, which are necessary for the synthesis of mitochondrial proteins. Since mtDNA is located in close proximity to ROS generation sites, and mitochondria have relatively simple DNA repair and protection systems, this type of DNA is particularly susceptible to mutations [13].

One of the causes of mitochondrial dysfunction is myocardial ischemia, which is accompanied by excessive mitochondrial fission and decreased mitochondrial fusion [14]. In addition to cardiomyocytes, endothelial cells of the arterial wall exhibit increased susceptibility to mitochondrial dysfunction due to their barrier and metabolic functions [2]. Therefore, studying the mechanism of mitochondrial dysfunction in cardiovascular diseases (CVD) is an important issue as it promotes developing strategies that directly target mitochondria in CVD [15].

This paper seeks to provide a thorough overview of the recent advancements in understanding the function and dysfunction of mitochondria. It focuses on the key potential mechanisms of oxidative stress and mtDNA mutations associated with the development of atherosclerosis and subsequent coronary heart disease (CHD) [13].

AIM

The study aims to determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis based on the analysis of research data and statistics from the MEDLINE, Scopus and Web of Science Core Collection electronic databases for 2007-2023.

MATERIALS AND METHODS

A comprehensive review of literature sources from the MEDLINE, Scopus, and Web of Science Core Collection electronic databases was conducted to critically analyse the data and determine the role of mitochondrial dysfunction in the pathogenesis of atherosclerosis.

REVIEW AND DISCUSSION

MITOPHAGY

The proper functioning of cardiomyocytes requires continuous coordination of mitochondrial function [12]. Given the high energy demands of cardiomyocytes that pump blood throughout the body under normal physiological conditions, dysregulation of mitochondrial homeostasis can lead to cardiac dysfunction and contribute to myocardial remodelling, resulting in the development of CVD and associated complications. Therefore, maintaining mitochondrial quality control in cardiomyocytes can facilitate improving cardiac function, preventing cardiomyocyte apoptosis, and mitigating the development of CVD. One of the mechanisms to control the quality of mitochondria is mitochondrial autophagy (mitophagy). Mitophagy repairs or removes dysfunctional and damaged mitochondria, thereby preserving their morphology, quantity, and function, ultimately promoting cell survival [16, 17].

Thus, mitophagy can be considered a mitochondrial 'quality check' process that prevents the accumulation of dysfunctional mitochondria, leading to the activation of inflammatory processes and cell death. Hypoxia and excessive generation of ROS serve as triggers for mitophagy in the heart [12].

IMPAIRMENT IN MITOPHAGY AS A DISRUPTION OF MITOCHONDRIAL HOMEOSTASIS

Mitochondrial homeostasis plays a crucial role in cells with a high level of energy consumption, as well as in the pathological development of CVD, in particular, atherosclerosis (6). Mitophagy is selectively used to remove defective mitochondria. However, if mitophagy is insufficient or if the mitochondrial damage is too severe, cell death eventually occurs [12, 18]. Therefore, a disruption in the mitophagy process and the increased accumulation of dysfunctional mitochondria lead to abnormal processes in cardiomyocytes and the subsequent development of CVD [19]. Impaired mitophagy specifically contributes to the progression of atherosclerotic lesions and endothelial cell apoptosis during thrombosis. Thus, understanding that the process of mitophagy contributes to the maintenance of

mitochondrial homeostasis may provide insights into the development of targeted therapies to address the failures in disordered systems [15].

MITOCHONDRIAL ROS

To date, oxidative stress has been recognized as a major factor contributing to the emergence and progression of atherosclerosis [20]. The term 'oxidative stress' refers to an imbalance between the production of ROS and the body's ability to neutralize reactive intermediates [21]. Under normal physiological conditions, the generation of ROS is tightly regulated through the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione reductase, and peroxidase [13]. Mitochondria are both a primary target of ROS and a key source of ROS production [22]. Mitochondrial dysfunction can lead to increased ROS production, which can mediate mtDNA malfunction, accumulation of oxidized low-density lipoproteins in the vessel wall, and stimulation of atherogenesis [23]. Therefore, the danger of ROS lies in the fact that they initiate a vicious cycle: ROS damage mitochondria whereas damaged mitochondria produce more ROS [24].

Mitochondria-generated ROS can modify numerous additional physiological pathways [25]. For instance, ROS can directly damage proteins by oxidation, or they can oxidize lipids to form lipid peroxidation products. ROS are also known to be involved in DNA damage, particularly, in mtDNA damage [26]. Furthermore, ROS can generate peroxynitrite from nitric oxide, causing intracellular nitrosylation and subsequent disruption of mitochondrial respiration, which is detrimental to normal cardiac function [13]. Therefore, the given data repeatedly emphasize that mitochondrial dysfunction is a key link in the pathogenesis of atherosclerosis, and increased ROS production may serve as a likely mediator of this process [24].

Mitochondrial ROS, associated with such risk factors as hyperglycemia and hypercholesterolemia, directly contribute to the formation of atherosclerotic plaques by inducing endothelial dysfunction, monocyte infiltration into the vessel wall, and enhancing endothelial cell apoptosis [6, 27]. The high reactivity of ROS leads to disturbances in the antioxidant balance and increased oxidative modification of the arterial wall [15].

Antioxidant systems, such as superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and others, constitute the first level of quality control and prevent molecular damage within the mitochondria [12]. However, when antioxidant systems are weakened or depleted, ROS are generated in large quantities, causing a cellular oxidative stress response [14].

Therefore, excessive production of ROS leads to cessation of energy production, increased cell death, irreversible oxidative damage to mtDNA, and alterations in gene expression. As a result, this contributes to the development and progression of cardiac dysfunction [14, 28].

MITOCHONDRIAL DNA MUTATIONS

The role of mitochondria in energy production makes them susceptible to damage from exposure to high levels of ROS, a byproduct of energy generation. Excessive ROS generation mediates damage and mutations in mtDNA: mtDNA mutations alter the structure of transferRNA (tRNA), causing disruptions in protein synthesis and leading to defective oxidative phosphorylation, further increase in ROS generation, and enhanced mtDNA mutations, forming a vicious cycle [14]. As mitochondrial functions depend on proteins encoded by both nuclear DNA and mtDNA, this indicates that mtDNA can be a potential target for therapeutic interventions. For instance, defective mtDNA sequences can be replaced to correct the mitochondrial gene and thus influence the disease [29].

Mutations in mtDNA can lead to heteroplasmy, a condition where multiple genome sequence variants coexist in a cell. The significance of this process becomes evident when the load of aberrant mtDNA copies determines the presence of mitochondrial dysfunction both in individual cells and tissues [18].

Furthermore, mutations in mtDNA lead to a decrease in tRNA levels and protein synthesis, including proteins involved in mitochondrial oxidative phosphorylation, as well as cause an increase in ROS production, which consequently results in mitochondrial oxidative stress and cell apoptosis. Conversely, elevated ROS levels typically induce more mtDNA mutations, particularly during its replication. In addition, impaired oxidative phosphorylation leads to reduced ATP production and disruption of mitochondrial membrane potential, altering the ATP/ADP ratio, interrupting normal ion flux, and stimulating glycolysis as an alternative pathway for ATP generation. Moreover, impaired Ca^{2+}metabolism can cause cytoplasmic and extracellular accumulation of Ca^{2+}, leading to cell swelling and death [8,16].

PHARMACOLOGICAL STRATEGIES FOR MITOCHONDRIAL FUNCTION MODULATION

Over the past two decades, a number of studies have been conducted to evaluate the pharmacological

strategies for mitochondrial function modulation. Since mitochondrial dysfunction plays a key role in the pathogenesis of CVD, it can be considered an intriguing target for the development of innovative treatment approaches [10].

The main strategies in mitochondrial dysfunction treatment involve the use of antioxidants and restoration of the respiratory chain and mitochondrial homeostasis [30]. The development of medications with enhanced antioxidant activity that specifically target mitochondria can be viewed as a key approach to the treatment of CVD rooted in oxidative stress. Furthermore, in new drug development, it is crucial to determine at which disease stages mitochondrial antioxidant therapy should be employed [6].

Contemporary research attempts are oriented towards the development of novel therapeutic strategies that impact mitochondrial function and the excessive production of ROS associated with atherosclerosis progression. Several therapeutic approaches have been analysed, including dietary interventions, physical exercise, and the use of medications targeting oxidative stress, inflammation, myocardial hypertrophy, fibrosis, and apoptosis. We can begin by considering that certain dietary interventions have been tested both in preclinical and clinical settings. It has been shown that polyphenols, such as flavonols, theaflavin, and epicatechin, are chemical compounds found in various natural sources, those being red wine, green tea, olive oil, and dark chocolate. Polyphenols are known to produce important antioxidant effects in numerous chronic disease treatments, including CVD. For example, quercetin reduces superoxide levels and increases urinary nitrate excretion, as well as enhances endothelial nitric oxide synthase activity and heme oxygenase-1 protein, which has antioxidant properties. Furthermore, polyphenols from olive oil and red wine reduce intracellular ROS levels, while epicatechin from green tea decreases the expression of proinflammatory molecules [31,32].

The cardioprotective effects of curcumin and resveratrol in improving the functional activity of mitochondria by inducing mitophagy have been elucidated in experimental models of atherosclerosis [33]. Chang et al. clearly reveal that natural antioxidants can effectively protect myocardial and endothelial cells from oxidative stress-induced damage by regulating mitochondrial quality control, and their safety and efficacy have been verified in numerous previous studies [30].

Oh et al. claim that urolithin A, a hydrolyzed metabolite of pomegranate formed by gut microbiota, serves as a potential target for mitochondrial dysfunction in the cardiovascular system due to its ability to promote mitophagy [34]. According to a study by Juan et al., urolithin A exhibited significant antiatherosclerotic and antiangiogenic properties by inhibiting endothelial cell migration and suppressing the expression of chemokine ligand 2 and interleukin-8 [35].

Another natural compound, spermidine, demonstrated cardioprotective properties by enhancing mitophagy. Spermidine is found in products such as broccoli, soybeans, and rice bran [36]. Oral administration of spermidine to aged mice models led to a reduction in interleukin-6 levels and improved the clinical presentation of atherosclerosis by regulating mitophagy [37]. Eisenberg et al. found that spermidine can be absorbed and accumulated in mouse cardiomyocytes, which indicates that spermidine may be a potential target in mitochondrial dysfunction [38]. Therefore, spermidine prevents mitochondrial dysfunction in CVD due to its pleiotropic pharmacological properties, which makes it a potential substance for further clinical research [7].

The use of carvedilol in patients with heart failure, due to its antioxidant and antiapoptotic properties, is particularly challenging in terms of its impact on mitochondrial dysfunction [31]. The study by Williams proved the ability of carvedilol to enhance cardiac mitochondrial biogenesis in vivo [39], which, in our opinion, is a crucial process for regulating energy balance and protecting myocardial and endothelial cells in critical conditions.

The studies of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers to improve mitochondrial dysfunction in experimental models showed that captopril can enhance mitochondrial biogenesis. Treatment with losartan and amlodipine effectively reduced arterial pressure in rats with spontaneous hypertension. Specifically, losartan was found to restore mitochondrial dysfunction and kidney damage by preserving glutathione and superoxide dismutase activities [31].

Statins, in addition to inhibiting endogenous cholesterol synthesis, have been revealed to exhibit important pleiotropic effects. In particular, they reduce oxidative stress in various tissues by targeting mitochondrial function. Thus, experimental studies by Parihar et al. proved that the administration of atorvastatin and simvastatin in rats resulted in decreased activity of mitochondrial nitric oxide synthase, cytochrome c release, and lipid peroxidation [31].

Metformin, as a first-line therapy for patients with type 2 diabetes, has demonstrated several beneficial effects on the cardiovascular system. Recent studies

have shown that metformin reduces the production of mitochondrial ROS, enhances the activity of antioxidant enzymes, and decreases inflammation associated with ischemia-reperfusion injuries [31]. Metformin is considered a safe clinical medication, with the most serious adverse effect being lactic acidosis. However, based on the results of numerous clinical studies, cases of acidosis are rare and are not solely associated with metformin use but also with complex patient conditions related to cardiovascular pathology [40]. Given the above, metformin is a promising target for addressing mitochondrial dysfunction in CVD.

Thus, in summary of the review, mitochondrial dysfunction is a clinical sign of early programmed cell death. These mitochondrial function impairments include changes in membrane potential and redox status, which are key features of healthy mitochondria [41]. Oxidative stress, increased mitochondrial permeability, pore opening, and excessive mitochondrial fission are the primary pathological processes of mitochondrial dysfunction, which should be targeted in the initial pharmacological therapy for atherosclerosis. To achieve this, numerous ongoing and new randomised clinical trials are required to further explore this area.

CONCLUSIONS

In this review, we have summarized the latest literature data on the association between mitochondrial dysfunction and the development of atherosclerosis. Mitochondria have been recognized as a novel therapeutic target in the development of atherosclerosis. However, the presence of current gaps in therapeutic strategies for mitochondrial dysfunction control still hinders clinical success in the prevention and treatment of atherosclerosis. Both antioxidants and gene therapy are appealing approaches to treating atherosclerosis. Nevertheless, further research is needed to determine the proper therapeutic strategy to reduce the impact of mitochondrial dysfunction on the progression of atherosclerosis.

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REVIEW ARTICLE

CONTENTS

Clinical classification of liver cirrhosis - a way to plan individual definitive treatment

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ABSTRACT

Aim: To develop clinical classification of liver cirrhosis, which can aid individualization and planning definitive treatment for this group of patients.

Materials and Methods: Computerized search of the literature was performed via PubMed using the following medical subject headings or keywords: "liver", "cirrhosis" and "classification"; or "liver", "cirrhosis" and "complications"; or "liver", "cirrhosis" and "treatment"; or "portal"", "hypertension" and "complications". Articles were independently evaluated by each author, the etiological, morphological and current clinical classifications of LC were analyzed, their advantages and disadvantages identified, and after discussion classification of LC was developed by consensus.

Conclusions: The developed clinical classification of liver cirrhosis will facilitate the planning of therapeutic tactics for each patient, allow to personalize the treatment of patients with this pathology.

KEY WORDS: liver cirrhosis, clinical classification, liver cirrhosis complications, portal hypertension

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INTRODUCTION

Liver cirrhosis (LC) is widely prevalent, rather common disease in the practice of both general practitioners and surgeons, and is the leading cause of death from liver diseases worldwide [1-5].

Different classification systems have been used for categorization of cirrhosis, focused on morphological and etiological features - small-nodular, large-nodular and mixed cirrhosis, and etiology - viral, alcoholic, toxic, autoimmune etc., amongst which Child-Pugh (CP) classification and the Model for End Stage Liver Disease (MELD) score are the most common [6,7]. While CP classification is widely used clinically and can give an indication of the severity of liver disease, the MELD score was developed and validated to predict mortality in patients with PH undergoing placement of transjugular intrahepatic portosystemic shunts (TIPS), but it is now more commonly used to predict survival in cirrhosis and for prioritization of patients for liver transplant. Undoubtedly, this is important information that a doctor needs to know. At the same time, it is important for a practitioner not only to establish the diagnosis of LC, but also to plan appropriate treatment.

Based on our many years of experience in treatment patients with LC, we have come to conclusion, that the formulation of a clinical diagnosis in this pathology should reflect the characteristics of the presence / absence of the main complications of the disease, with assessment of their severity.

AIM

The aim of our study was to develop clinical classification of LC, which can aid individualization and planning definitive treatment for this group of patients.

MATERIALS AND METHODS

Computerized search of the literature was performed via PubMed using the following medical subject headings or keywords: "liver", "cirrhosis" and "classification"; or "liver", "cirrhosis" and "complications"; or "liver", "cirrhosis" and "treatment"; or "portal"", "hypertension" and "complications". The following criteria were applied for study inclusion: publication in peer-reviewed journals, and publication since 1980. Articles were independently evaluated by each author, the etiological, morphological and current clinical classifications of LC were analyzed, their advantages and disadvantages identified, and after discussion classification of LC was developed by consensus.

REVIEW AND DISCUSSION

We emphasize that there is no LC without portal hypertension (PH), but the severity of its clinical manifestations are determined by the degree of morphological changes in the liver. Therefore, the diagnosis of cirrhosis should reflect this syndrome and its complications. Liver dysfunction is present at all stages of cirrhosis.

Based on the above, the clinical classification of LC can be presented as follows (with brief description of points):

1. Liver cirrhosis:
1.1. The stage of compensation
1.2. The stage of parenchymal decompensation.
1.3. The stage of vascular decompensation.
1.4. The stage of parenchymal-vascular decompensation.
1.5. The stage of hepatocerebral decompensation.
2. Portal hypertension ((mild or clinically significant portal hypertension (CSPH)):
2.1. Splenomegaly.
2.2. Gastroesophageal varices (GOV) (small, medium, large; type 1or 2); isolated gastric fundal varices (IGV) (type 1or 2).
2.3. Portal hypertensive gastropathy (PHG) (mild, severe).
2.4. Hypersplenism syndrome.
3. Complications of liver cirrhosis:
3.1 Ascites: uncomplicated (mild, moderate, large), refractory (diuretic resistant, diuretic intractable).
3.2. Gastrointestinal bleeding.
3.3 Jaundice.
3.4. Hepatic encephalopathy (HE).
3.5. Hepatorenal syndrome (HRS) (type 1 or 2).
3.6. Spontaneous bacterial peritonitis (SBP).
3.7. Hyponatremia (hypovolemic, hypervolemic).
3.8. Hepatic hydrothorax (HH).
3.9. Hepatopulmonary syndrome (HPS).
3.10. Portopulmonary hypertension (PPHTN).
3.11. Chronic liver failure (CLF) ((slowly progressive or acute exacerbative type (include acute-on-chronic liver failure (ACLF)).

Patients with cirrhosis without any symptoms are termed to have compensated cirrhosis. Complications such as ascites, variceal bleeding, hepatic encephalopathy, or non-obstructive jaundice, which can develop with cirrhosis of any origin, herald the onset of decompensated cirrhosis [3]. In the stage of compensation, additionally to the typical liver abnormalities, esophageal /gastric/gastroesophageal varices may not be present yet, or low grade varices may be present. On esophagogastroduodenoscopy (EGDS), esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted. It was recommended that the size classification be as simple as possible, i.e., in 2 grades (small and large), either by semiquantitative morphological assessment or by quantitative size with a suggested cut-off diameter of 5 mm, with large varices being those greater than 5 mm. When varices are classified in 3 sizes–small, medium, or large–as occurs in most centers by a semiquantitative morphological assessment (with small varices generally defined as minimally elevated veins above the esophageal mucosal surface, medium varices defined as tortuous veins occupying less than one-third of the esophageal lumen, and large varices defined as those occupying more than one-third of the esophageal lumen) [8].

According Sarin classification, especially useful in describing the distribution of varices in the distal esophagus and stomach, fundal varices are included in two groups: GOV 2, when the esophageal and fundal varices are present in continuity over the cardia, which might include IGV 1 that are usually isolated gastric fundal varices. GOV 1 are typically a continuation of esophageal varices into the lesser curvature varices. IGV 2 are gastric varices at ectopic sites in the stomach outside the cardiofundal region or the first part of the duodenum. [9,10].

However, there is splenomegaly already present, increase in the diameter of the portal and splenic veins with an abnormal blood flow in them due to existing PH.

The stage of parenchymal decompensation is determined when the patient has ascites and/or parenchymal jaundice along with clinical manifestations of the disease.

The International Ascites Club proposed to link the choice of treatment of uncomplicated ascites to a classification of ascites on the basis of a quantitative criterion [11]. Uncomplicated ascites is the ascites that is not infected and which is not associated with the development of the HRS. Ascites can be graded as follows:

grade 1 (mild) - ascites is only detectable by ultrasound examination; grade 2 (moderate) - ascites causing moderate symmetrical distension of the abdomen; grade 3 (large) - ascites causing marked abdominal distension.

Refractory ascites is the ascites that cannot be mobilized or early recurrence of which (that is, after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. This includes two different

subgroups: diuretic resistant ascites - ascites that is refractory to dietary sodium restriction and intensive diuretic treatment (spironolactone 400 mg/day and frusemide 160 mg/day for at least one week, and a salt restricted diet of less than 90 mmol/day (5.2 g of salt/day); diuretic intractable ascites–ascites that is refractory to therapy due to the development of diuretic induced complications that preclude the use of an effective diuretic dosage [11].

The stage of vascular decompensation is diagnosed when there is acute variceal bleeding. However, the doctor should remember that the presence of rectal (hemorrhoid) bleeding or metrorrhagia in a patient can also be clinical manifestations of PH due to already formed LC.

The stage of parenchymal-vascular decompensation is determined when the patient has signs of a combination of bleeding and ascites. This is a rather severe group of patients that requires a special approach to treatment.

The stage of hepatocerebral decompensation is determined when manifestations of HE are present. HE is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma [12, 13]. According West Haven criteria (WHC) used for grading HE, in grade I, patients show trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm. Despite oriented in time and space the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination, or to the caregivers. In grade II, lethargy or apathy, disorientation for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year), obvious personality change, inappropriate behavior, dyspraxia, asterixis are present. In grade III, patients may have somnolence to semi-stupor, they are responsive to stimuli, confused, gross disorientation is present, bizarre behavior may be demonstrated. Patients are also disoriented for space (at least three of the following wrongly reported: country, state (or region), city or place). In grade IV, patients are in coma and does not respond even to pain stimuli. When it became obvious that patients without clinical signs of HE may show alterations of brain function in neuropsychological or neurophysiological measures, a fifth grade was added to this system: the so-called subclinical or minimal HE (MHE). In this grade, psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change are present. Some experts have recommended that MHE and grade I HE be combined and classified as "covert HE" that contrasts to "overt" HE with clinical grades 2–4 [12].

PH is defined as an increase of portal pressure (PP) > 5 mmHg. The gold standard to measure portal venous pressure is the evaluation of hepatic venous pressure gradient (HVPG). Based on PP, patients with LC can be divided into those with mild PH (HVPG > 5 but < 10 mm Hg) and those with CSPH, defined by an HVPG ≥10 mm Hg, which is associated with an increased risk of complications like gastrointestinal varices, ascitic decompensation, gastrointestinal hemorrhage from portal hypertensive collaterals and HE [14,15].

PHG is diagnosed by characteristic endoscopic findings of small polygonal areas of variable erythema surrounded by a pale, reticular border in a mosaic pattern in the gastric fundus/body in a patient with cirrhotic or non-cirrhotic PH. The Baveno scoring system uses point calculations to define PHG as mild (≤ 3 points) vs severe (≥ 4 points) and also adds gastric antral vascular ectasia into the classification [16].

A serious complication of LC is secondary hypersplenism syndrome, which is defined by a combination of splenomegaly and peripheral blood pancytopenia. Its characterization allows assessing the severity of the patient's condition.

HRS is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure [17]. Type 1 HRS is a rapidly progressive acute renal failure that frequently develops in temporal relationship with a precipitating factor for a deterioration of liver function together with deterioration of other organ function. Type 2 HRS occurs in patients with refractory ascites and there is a steady but moderate degree of functional renal failure, often with avid sodium retention. Patients with type 2 HRS may eventually develop type 1 HRS either spontaneously or following a precipitating event such as SBP [17].

SBP is a very common bacterial infection in patients with cirrhosis and ascites. The diagnosis of SBP is based on diagnostic paracentesis. Patients with SBP may have one of the following: local symptoms and/or signs of peritonitis (abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus); signs of systemic inflammation (hyper or hypothermia, chills, altered white blood cell count, tachycardia, and/or tachypnea); worsening of liver function; HE; shock; renal failure; and gastrointestinal bleeding. However, it is important to point out that SBP may be asymp-

tomatic, particularly in outpatients [11].

In patients with LC hyponatremia is defined when serum sodium concentration decreases below 130 mmol/L, but reductions below 135 mmol/L should also be considered as hyponatremia, according to recent guidelines on hyponatremia in the general patient population [18]. Hypervolemic hyponatremia is the most common and is characterized by low serum sodium levels with expansion of the extracellular fluid volume, with ascites and edema. By contrast, hypovolemic hyponatremia is less common and is characterized by low serum sodium levels and absence of ascites and edema, and is most frequently secondary to excessive diuretic therapy.

HH is defined as a pleural effusion, typically more than 500 mL, in patients with LC without coexisting underlying cardiac or pulmonary disease [19,20].

HPS is defined as the triad of liver dysfunction, intrapulmonary vasodilation and arterial oxygenation defect, which prevalence varies from 10% to 17% in the cirrhotic population and is associated with increased mortality [21].

PPHTN is a well-recognized complication of cirrhosis, defined as pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) in a patient with coexisting portal hypertension and no other alternative cause of pulmonary hypertension [21].

In patients with cirrhosis, the annual incidence of HCC is about 3%-5%, which require special treatment, such as local liver resection, liver transplantation, ablation therapy and chemotherapy [21].

Patients with decompensated cirrhosis, because of complications or other factors, may experience either acute deterioration of liver function or slowly progressive disease. Acute deterioration of liver function is defined as the total bilirubin ≥ 171 μmol/L and prothrombin activity ≥ 40%. Accordingly, CLF can be divided into two types: slowly progressive, equivalent to the current slow progression of decompensated LC in patients with HE, and acute exacerbative type, equivalent to deterioration that occurs in decompensated LC, might include the ACLF proposed by EASL, which is more serious yet [22]. ACLF is defined as a syndrome characterized by acute decompensated cirrhosis, associated with the failure of various organs and a high short-term mortality rate (mortality at 28 days ≥15%) [23,24]. The Sequential Organ Failure Assessment (SOFA) score, was adapted to the characteristics of patients with cirrhosis and was called CLIF-SOFA, or its simplified version, CLIF-C Organ Failure score (CLIF-C OF). The presence of ACLF is identified according to the number and type of organ failure, while its severity is classed into 3 stages No ACLF is defined as no organ failure or 1 single organ failure, not including kidney failure, with serum creatinine <1.5mg/dL present and no hepatic encephalopathy. ACLF grade 1 is assumed if there is only one single kidney failure or 1 single organ failure linked to kidney failure (creatinine between 1.5 and 1.9mg/dL) or level 1–2 hepatic encephalopathy present. ACLF grade 2 is characterized by 2 organ failures, ACLF grade 3 – when ≥3 organ failures are present [24, 25].

According the classification we proposed above, the clinical diagnosis of LC patient is formulated with the stage of the disease, the presence/absence of CSPH and PH related complications (complication, its type/degree), complications of LC (complication, its type/degree).

For example, patient with LC in stage of compensation, PH (non CSPH) and splenomegaly require lowering portal pressure and prevention of complications by administration of non-selective β-blockers, EGDS repetition in 1 to 3 years, patient education (nutrition, physical exercises, safety of alcohol and medications, immunizations), screening for routine cancers and associated comorbidities.

Patient with LC in stage of parenchymal decompensation, CSPH, splenomegaly, uncomplicated moderate ascites requires symptomatic relief via a low-sodium diet and diuretics.

For patient with LC in stage of parenchymal decompensation, CSPH, splenomegaly, refractory diuretic resistant large ascites, HH control of ascites through large-volume paracentesis with albumin replacement, symptomatic relief by thoracentesis will be indicated. TIPS also could be considered, because it may be beneficial as for refractory diuretic resistant ascites, so for HH.

Patient with LC in stage of parenchymal-vascular decompensation, CSPH, splenomegaly, refractory diuretic resistant large ascites, medium-large GOV type 2, complicated by gastroesophageal bleeding, SBP require cautious transfusion in stable patients after volume resuscitation, hemostatic treatments (vasoactive and endoscopic), large-volume paracentesis with albumin replacement, intravenous antibiotics selected on the basis of local experience and risk of multidrugresistant bacteria.

CONCLUSIONS

In our opinion, the proposed above clinical classification of LC, will facilitate the planning of therapeutic tactics for each patient, which will allow to personalize the definitive treatment of patients with this pathology.

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CASE STUDY

CONTENTS

The course of COVID-19 in a multiple sclerosis: a case report

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ABSTRACT

The authors present the case of a prolonged course of COVID 19 disease in a 37-year-old patient with multiple sclerosis on anti-CD20 monoclonal antibodies immunotherapy.

This publication presents a clinical case of the course of COVID-19 disease in a multiple sclerosis patient receiving ublituximab therapy. The use of disease-modifying anti-CD20 monoclonal antibody therapy was associated with a protracted wave-like course of COVID-19 with the addition of a bacterial infection. This publication illustrates the key mechanisms and approaches to the treatment of such a cohort of patients.

The use of highly effective multiple sclerosis treatment methods may be associated with an increase in the incidence of COVID-19 and worsening of its course. Multiple sclerosis patients receiving anti-CD20 therapy are at particular risk of a wave-like course of COVID-19, caused by immunosuppression, creates a basis for bacterial and fungal coinfection.

KEY WORDS: immunotherapy, COVID-19, multiple sclerosis, monoclonal antibody therapy

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INTRODUCTION

The course and treatment of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may have significant specific features in patients with multiple sclerosis (MS), causing additional risks of severe course of the disease with development of acute respiratory distress syndrome (ARDS) [1].

Population-based data indicate significantly increased risk of severe course of disease and mortality from COVID-19 in patients with MS [2]. On the contrary, in other studies the course of COVID-19 and mortality depended mostly on age and co-morbidities, such as obesity, diabetes, heart and lung diseases [3]. Furthermore, it is assumed that there is an associative relationship between the adverse course of COVID-19 and progressive course of MS, higher rate of disability and certain methods of treatment, in particular, the chronic use of immunosuppressive agents [4]. Although MS is mostly diagnosed in young patients, in clinical practice there are many 60+ patients with MS.

Modern immunomodulatory therapy for MS, treatment with immunosuppressive drugs in particular, can increase the risk of an infectious process, especially with regard to viruses and development of bacterial coinfection [5]. A target therapy for MS, including the use of anti-CD20 monoclonal antibodies, is primarily aimed at the suppression of immune response. Hence, patients may become more prone to complications caused by COVID-19 due to an insufficient immune system response to the virus. However, immunosuppression has been reported to play a protective role against COVID-19 and its severe course in MS patients treated with anti-CD20 agents [6].

This paper presents a clinical case of COVID-19 in a patient with MS treated with ublituximab (a humanized monoclonal antibody targeting the CD20 B-lymphocyte antigen), who had a protracted wave-like course of the disease with prolonged SARS-CoV-2 replication [7].

CASE REPORT

Patient N., 37 years o/age, Caucasian, diagnosed with secondary progressive MS (according to the McDonald criteria [8]) in 2016. She received pulse therapy with methylprednisone (years 2016-2018), and disease-modifying therapy with glatiramer acetate and fingolimod (years 2018-2020). In January 2020, due to a highly active course of MS, and considering the current evidence [9, 10], treatment with ublituximab was initiated (one injection was done). The prescribed treatment favored the absence of exacerbation and neuroradiological stabilization of MS (Expanded Disability Status Scale (EDSS) [11] = 2 points).

On 19 March 2021, the patient developed a sore throat, fever up to 37.6°C, SARS-CoV-2 was detected by PCR, and COVID-19 was diagnosed. From day one until day 17 of the disease she was under the outpatient supervision, receiving amoxicillin protected with clavulanic acid for 7 days, and then 400 mg moxifloxacin for 10 days. The patient was admitted to the hospital for further treatment on day 18 of the illness due to hectic hyperthermia, which was not corrected with antipyretic drugs within the last 5 days, shortness of breath with a decrease in saturation according to pulse oximetry data (SpO_2 89-90 %), combined with asymptomatic episodes of atrial fibrillation (according to ECG monitoring data). The patient had positive repeated PCR test for SARS-CoV-2. Spiral computed tomography (CT) of the lungs showed viral bilateral pneumonia, with the pronounced pathological changes in 25-50 % of the lung parenchyma (stage 2 [12]; Fig. 1). Taking into account the severity of the patient's condition, a critical decrease in the absolute count of lymphocytes to $0.4x10^9$/l, intravenous administration of human immunoglobulin in a dosage of 32 g (0.4 g/kg/day) and pulse therapy with methylprednisone 750 mg per day for 3 days was prescribed, with the following gradual reduction of the daily dose to 40 mg. Since PCR test was positive, antiviral drug remdesivir was prescribed intravenously for 4 days according to the regimen: a loading dose of 200 mg/day on day 1, followed by 100 mg/day. Concomitant heparin, antiarrhythmic drugs, antibiotics (taking into account the significant increase in procalcitonin values), prophylactic antifungal treatment were used.

In the course of treatment, the patient showed normalization of the inflammatory markers' levels, body temperature decreased to 36.6°C, SpO_2 increased to 96 %, and general

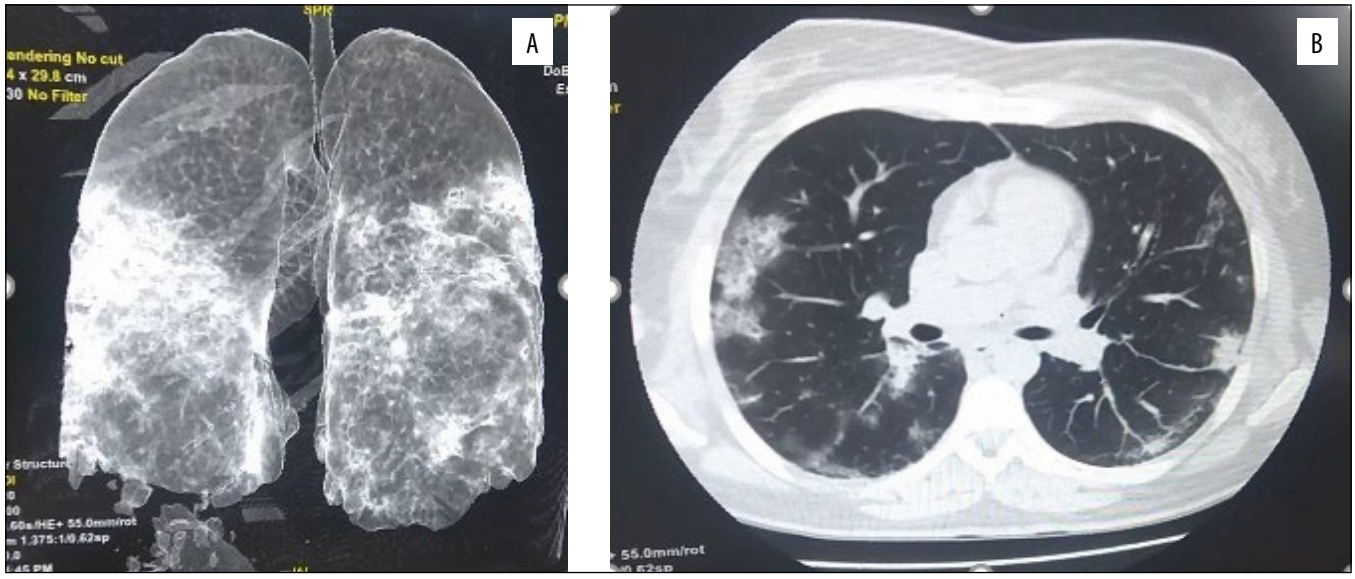

Fig. 1. Lung CT scan of the patient N. (day 18 of illness), demonstrating the signs of viral bilateral pneumonia, with involvement of 25-50 % of the lung parenchyma (stage 2 [12]). (A) 3D reconstruction; (B) axial plane.

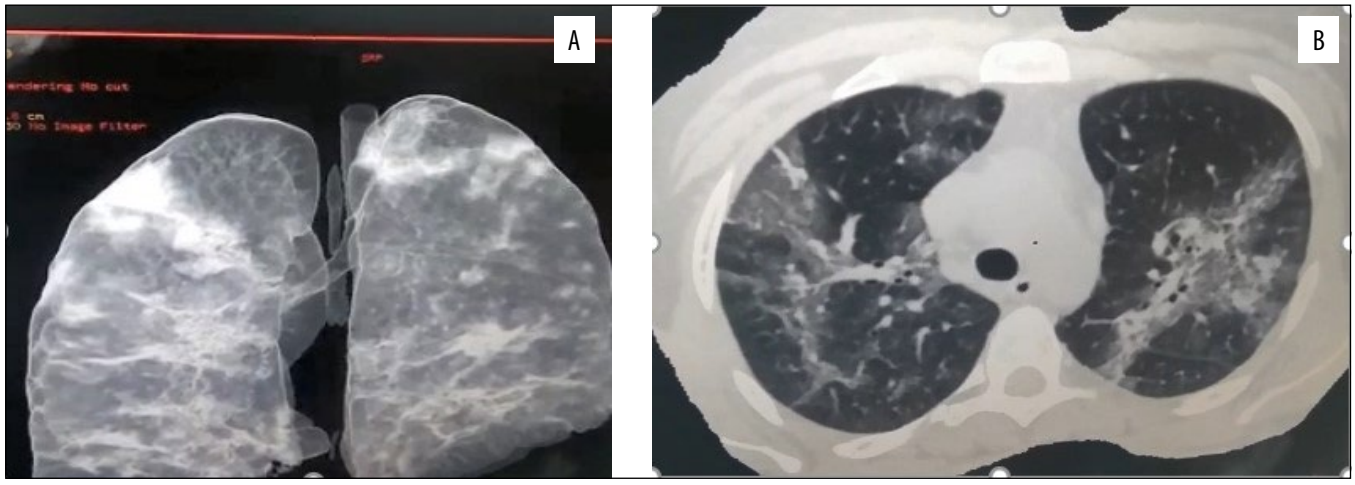

Fig. 2. Lung CT scan of the patient N. (day 32 of illness), demonstrating the signs of viral bilateral pneumonia with coalescent foci, with involvement of 50-75 % of the lung parenchyma (stage 3 [12]). (A) 3D reconstruction; (B) axial plane.

weakness regressed. On day 26 of the illness, the patient was transferred to the daytime in-patient ward, where she received anticoagulant rivaroxaban and antiarrhythmic agent, while the dose of steroids was further gradually reduced.

However, on day 32 of disease, the patient was re-admitted to the hospital with complaints of shortness of breath, a decrease in SpO_2 to 88-90 %, and an increase in body temperature up to 38.5°C. PCR testing revealed again a positive result for SARS-CoV-2. The increased inflammatory markers indicated exacerbation of the disease, while repeated CT of the lungs revealed bilateral viral pneumonia with coalescent foci with damage of 50-75 % of the lung parenchyma (stage 3 [12]; Fig. 2). Considering the severity of the condition and the data of clinical, laboratory and instrumental evaluation, the patient was repeatedly given pulse therapy with methylprednisone 500 mg for 3 days, followed by a gradual dose reduction, and antiviral therapy with remdesivir for 3 days according to the regimen described above. Additionally, meropenem and fluconazole were prescribed. Upon re-admission to the hospital, the patient had her blood culture tested for sterility, with no bacterial growth found.

The patient's condition improved on day 42 of the disease: shortness of breath, general weakness and fatigue regressed, while pro-inflammatory blood markers, such as C-reactive protein, ferritin, fibrinogen, interleukin-6, procalcitonin, got back to normal. However, repeated PCR test for SARS-CoV-2 was negative only on day 52. The patient was discharged home under the supervision of a family doctor and a neurologist with adherence to quarantine measures. After the viral infection, the patient had no signs of clinical and neuroradiological MS activity. Blood test for the subpopulation of lymphocytes, conducted on 4 April 2021, showed a slight increase in the relative and absolute count of B-lymphocytes (CD3-CD19+) up to 0.9 % (10 cells/**μL**). Due to this it was decided to postpone administration of the next doses of ublituximab.

It has been suggested that immunocompromised individuals, particularly MS patients receiving immunosuppressive therapy to modify the course of the disease, are at increased risk of developing severe COVID-19 [13, 14]. However, many patients receiving immunosuppressive therapy for MS, have uncomplicated COVID-19. Patients with MS and a severe form of COVID-19 are usually older and, accordingly, have a greater number of comorbidities, including the decompensated ones. At present, several immunosuppressive drugs for COVID-19 treatment are being tested, such as fingolimod (a S1P modulator) and emapalumab (an anti-interferon-gamma monoclonal antibody) [15]. Trials of tocilizumab (an antagonist of interleukin-6 receptors) have been completed for the treatment of severe forms of COVID-19 [16], and now it is included in the international guidelines as an effective drug for the therapy of patients with SARS-CoV-2 infection progression, including those with MS [17, 18].

In MS patients receiving immunomodifying therapy, the ability of the drugs to suppress the hyperactive cascade reaction of the immune system should be considered. Taking into account the mechanism of action of almost every monoclonal antibody used to treat MS, some of them should contribute to a mild, uncomplicated course of COVID-19 [19]. During SARS-CoV-2 infection, a powerful expressive immunological response occurs with massive production of pro-inflammatory cytokines (in particular, interleukin-6), which triggers the development of a «cytokine storm» and ARDS [20]. Data were obtained on the positive effect of interferon-beta medications in the treatment of COVID-19, especially in the case of their early adminisration [21]. Glatiramer acetate and fumarate, which are used to treat MS, increase the expression of circulating natural killer cells, providing additional protection against COVID-19 and its severe course in such patients [22]. The effect of glatiramer fumarate in inhibiting the function of macrophages, which play an important role in the development of ARDS, is also considered [1].

There is still insufficient evidence for the effectiveness of anti-B cell therapy in patients with MS and COVID-19. However, studies on ocrelizumab drug noted a high risk of addition and development of bacterial infections [23]. It is not fully understood whether there is a temporal relationship between the use of ocrelizumab and the risk of infection with COVID-19 and the severe course of the disease. Some studies indicate the risks of severe disease, with increased need for an in-hospital treatment, but no increase in mortality [18, 24, 25]. The use of ocrelizumab results in CD20+ B-lymphocytes depletion, which, in turn, leads to a decrease in cytokine production, a decrease in antigen-presenting function and differentiation of B-lymphocytes into plasma cells [26].

Initial antiviral immune responses are provided primarily by T-cells, in particular CD8+ cytotoxic T-lymphocytes, natural killer cells and, to a lesser extent, B-cells [27]. This allows us to explain why patients receiving anti-CD20 therapy have a relatively good response to treatment of viral infections, but on the other hand, the addition of a bacterial infection complicates the recovery process. Ocrelizumab and other anti-CD20 agents have relatively insignificant effect on T-cell counts and have not been associated with severe viral infections [28]. In the registration studies of MS treatment with ocrelizumab, infections were slightly more frequent compared to similar groups (interferon-beta-1a or placebo) [29]. In these studies, the viral infection that could be identified was mild-to-moderate. Infections were most likely bacterial, i.e. pneumonia, urinary tract infections and cellulitis. However, there are always rare exceptions to the rule; for example, an individual case of fulminant hepatitis

associated with an unusual ECHO virus-25 infection in a patient receiving ocrelizumab therapy [30].

The clinical case described above shows a prolonged course of COVID-19 with pneumonia, relapses of the immunopathological phase of the disease and the addition of bacterial superinfection, which may have been caused by the use of immunomodulatory therapy in connection with the underlying disease and longer replication of the virus. The use of ublituximab can lead to depletion of B-cells, which, in turn, impairs the formation of anti-SARS-CoV-2 antibodies. Regarding the further treatment of MS, the existing guidelines indicate a delay in the re-administration of immunosuppressive drugs, and vaccination is not a contraindication to its implementation [1].

CONCLUSIONS

The use of highly effective MS treatment methods may be associated with an increase in the incidence of COVID-19 and worsening of its course. MS patients receiving anti-CD20 therapy are at particular risk and require careful clinical evaluation and consideration of an atypical immune response with the formation of a protracted course of the disease. Such a wave-like course of COVID-19, caused by immunosuppression, creates a basis for bacterial and fungal coinfection. However, immunosuppression with anti-CD20 drugs does not exclude the possibility of pulse therapy with steroids. What concerns the following MS treatment, guidelines suggest a delay in re-administration of immunosuppressive drugs, and vaccination against COVID-19 makes sense after six months with subsequent antibody testing.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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CASE STUDY

CONTENTS

Relation of *Streptococcus Pyogenes* tonsillitis isolate to antimicrobial agents and its infection treatment

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ABSTRACT

We reported the case of tonsillitis treatment in a 17-years-old boy with use of chemical non-antibiotic preparations, plant derived products and antibiotic benzathine phenoxymethylpenicillin. The antimicrobial agents for treatment were selected on the basis of their activity against a disease agent, the group A *β*-hemolytic strain *Streptococcus pyogenes* BS1 isolated from a patient.

The bacterium was susceptible *in vitro* to β-lactams, with largest zones conditioned by penicillin G and benzathine phenoxymethylpenicillin discs, to fluoroquinolones and to cephems, with exception of cefazolin. Lincosamide clindamycin, macrolide spiramycin, aminoglycoside gentamicin, erythromycin, tetracycline and combination of sulfamethoxazole and trimethoprim were inactive against this bacterium. The *Streptococcus pyogenes* BS1 demonstrated intermediate susceptibility to the cephalosporin cephalexin, fluoroquinolone lomefloxacin and glycopeptide vancomycin.

Non-antibiotic preparations were evaluated against *Streptococcus pyogenes* BS1 also. Among them "Stomatidin", "Chlorophyllipt", and phages of "Pyofag" were more effective than "Decatylen", "Decasan" and "Furadonin" *in vitro.*

The antimicrobial applications of "Stomatidin", "Chlorophyllipt" and phages of "Pyofag" in the patient were less effective compared to the result of antibiotic benzathine phenoxymethylpenicillin treatment. Complete recovery of the patient was achieved with use of this antibiotic and *Calendula* flower extract as an local anti-inflammatory agent.

KEY WORDS: *Streptococcus pyogenes,* antibiotics and non-antibiotic preparations, susceptibility, resistance, tonsillitis treatment, 17-years-old boy

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INTRODUCTION

Streptococcal sore throat, strep throat also known as tonsillitis is a common bacterial infection. It is most spread in children, accounting 20%–30% sore throat visits to doctors, and less in adults, comprising 5%–15% of sore throat visits. The *β*-hemolytic *Streptococcus pyogenes* causes from 15 to 30% of all pharyngitis in children [1]. It is generally accepted that children cohorts from 5 to 15 years are most vulnerable to the disease.

β-lactams are usually applied in the treatment of strep throat infection, with macrolides being used for patients allergic to β-lactams.

However, reduced susceptibility to β-lactams [2] and resistances to penicillin [3], to cephalosporins ceftriaxone, macrolide erythromycin, lincosamide clindamycin, tetracycline, amphenicol chloramphenicol, fluoroquinolone levofloxacin [4, 5] were detected in *S. pyogenes*. Up to one-third of patients treated for group A Streptococcus pharyngitis fail to respond to antibiotic therapy [3].

Throat lozenges containing antimicrobial quaternary ammonium compound, dequalinium chloride [6], antiseptic and local anesthetic hexylresorcinol [7] demonstrated effectiveness in treatment of acute sore throat.

Some plant products are able to suppress the growth of *S. pyogenes*. Most often such activity were reported in compounds containing aromatic rings [8]. Particularly, hot water infusions from licorice root, barberry root, thyme, and oregano flowering shoots that contain such compounds may provide potential sources for developing remedies against *S. pyogenes* infections [9]. List of medicinal plants producing compounds active against *Streptococcus pyogenes* contains 82 species [10].

On human tissue *Streptococcus pyogenes* is able to form biofilms that contribute to mechanisms of the bacterium resistance to antibiotics and antibiotic treatment failure [11]. Bacteriophage-encoded endolysin PlyC diffuses through the extracellular material constituting the bacterial biofilm and lyses the *Streptococcus pyogenes* cells within the biofilm matrix [12]. In contrast

to antibiotics, bacteriophages act specifically against particular microbes and, usually, have no harmful effect on normal microbiota of humans [13].

In this article we reported about treatment of tonsillitis in 17-years old boy with use of several non-antibiotic medications (synthetic chemicals, plant derived products and phages preparation) that only alleviated symptoms, and antibiotic benzathine phenoxymethylpenicillin application, that finally lead to the complete recovery of the patient.

CASE REPORT

17 years old boy experienced fever (temperatures above 38°C), sore throat, palatine tonsils enlargement to above 75% of the oropharyngeal width, the grade +4 , according to tonsil size grading by Brodsky and co-workers [14] and redness with typical tonsillar exudate, pain with swallowing and enlarged lymph nodes in the front of the neck. The blood analysis results, provided by the clinical laboratory, demonstrated an increase in lymphocytes to 46 per 100 of leucocytes (Table 1). The spleen and liver were not enlarged, suggesting no viral glandular fever.

The rapid antigen detection test (using a kit of AMEDA Labordiagnostik GmbH (Austria) was positive. The microscopy of the exudate demonstrated Gram-positive streptococci. The bacterium, cultured from exudate, was catalase-negative in catalase test [15]. It was sensitive to 0.04 IU of the bacitracin in the CLSI disc diffusion test. The β-hemolysis was observed around streptococcal colonies seeded from a throat swab and grown onto sheep blood agar at 37°C for 1 day [16]. The isolate was identified as group A β-hemolytic *Streptococcus pyogenes* and given the strain number BS1.

Susceptibility of *Streptococcus pyogenes* BS1 to antibiotics (Table 2) was studied in a disc diffusion test, using discs from HiMedia Laboratories Pvt. Limited (India) and Liofilchem Inc (USA).

To test other antimicrobials for antistreptococcal activity, sterile Whattman №1 paper discs (6 mm in diameter) were impregnated with solutions of these antimicrobial agents using 5 μL pipette to give comparable concentrations of active ingredients per disc. These discs were dried in sterile air flow each time before the next drop of the solution application. By this way the discs were prepared from preparations "Stomatidin" (chlorhexidine, 1 mg/ml), Bosnalijek d. d., (Bosnia and Herzegovina), "Chlorophyllipt" (ethanol extract of chlorophylls A and B from *Eucalyptus viminalis,* 10 mg/mL), Halychfarm (Ukraine), "Furadonin" (nitrofurantoin) tablets Olainfarm, (Latvia), "Decatylen" lozenges (0.25 mg dequalinium chloride/0.03 mg cinchocaine hydrochloride) Merckle GmbH (Germany), "Decasan" (0.02% decamethoxine solution, inhalation antiseptic) YURiA Pharm (Ukraine) (Table 3).

The *Pelargonium sidoides* roots ethanol extract Eps® 7630 (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), and Calendulae flos (*Calendula* flowers extract in 70% ethanol, 1:10) (LLC DKP Pharmaceutical factory, (Ukraine) were applied as 20 μL drops on Petri dishes medium in advance of lawns inoculation. The "Pyofag", a suspension of phages, including specific to *Streptococcus pyogenes*, "Pharmex Group" LLC (Ukraine) was applied as 20 μL drops onto the fresh seeded lawns.

All discs were placed onto lawns of *Streptococcus pyogenes* BS1 fresh-seeded on the blood-agar with broth night culture. The inhibition zones (Table 2) were evaluated after 1 day of the Petri dishes incubation at 37°C according to CLSI standards [17].

The isolate *Streptococcus pyogenes* BS1 was most sensitive to β-lactams, susceptible to all tested penicillins with largest zones conditioned by penicillin G and benzathine phenoxymethylpenicillin (Table 2). It also demonstrated good sensitivity to fluoroquinolones and to cephems, with exception of cefazolin. Lincosamide clindamycin, macrolide spiramycin and aminoglycoside gentamicin produced zones 10 mm in diameter or less and were regarded as inactive against our isolate. Application of discs containing erythromycin, tetracycline and combination of sulfonamide antibiotic sulfamethoxazole and trimethoprim, a dihydrofolate reductase inhibitor, resulted in no zones formation in the lawns evidencing resistance of isolated strain to these antibiotics. The *Streptococcus pyogenes* BS1 demonstrated intermediate susceptibility to the cephalosporin ceph-

Table 1. White blood cell distribution in blood of the patient

White blood cell line	Cells before treatment, %	Cells after treatment, %
Neutrophils	45	50
Lymphocytes	46	37
Monocytes	8	8
Eosinophils	1	4
Basophils	0	1

Table 2. Sensitivity of *Streptococcus pyogenes* BS1 to antibiotics

Antimicrobial agent	Applied disc content	*Mean inhibition zones in bacterial lawns, mm
Penicillins		
Amoxicillin	30 μg	24 S
Amoxicillin/Clavulanic acid	20/10 μg	23 S
Ampicillin/cloxacillin	10 μg	25 S
Ampicillin/sulbactam	10 μg	24 S
Ampicillin	10 μg	25, S
Penicillin G	10 IU	27, S
Benzathine phenoxymethylpenicillin	10 μg	27, S
Macrolide		
Azithromycin	15 μg	18, S
Erythromycin	15 μg	No zone, R
Spiramycin	100 μg	7 R
Oleandomycin Oxoid	15 μg	25 S
Roxithromycin	15 μg	26 S
Cephems		
Cephotaxim	30 μg	25,S
Cefoperazone	75 μg	24, S
Cefixim	5 μg	15, S
Cefazolin	30 μg	16, R
Cephalexin	30 μg	20, I
Lincosamides		
Clindamicin	2 μg	10, R
Aminoglycoside		
Gentamycin	10 μg	10, R
Fluoroquinolones		
Lomefloxacin	10 μg	19, I
Moxifloxacin	5 μg	18, S
Norfloxacin	10 μg	20, S
Ofloxacin	5 μg	17, S
Tetracyclines		
Tetracyclin	30 μg	No zone, R
Diaminopyrimidine/sulfonamide (1:19)		
Trimethoprim/sulfametoxazole	1.25/23.75 μg	No zone, R
Glycopeptide		
Teicoplanin	30 μg	26 S
Vancomycin	30 μg	12, I
Polypeptide		
Bacitracin	0.04 IU	16 S

*Relation of isolate to antibiotics according to CLSI standards [17]: S - susceptible, I - intermediate susceptibility, R – resistant.

alexin, fluoroquinolone lomefloxacin and glycopeptide vancomycin.

The *Streptococcus pyogenes* BS1 was sensitive to antimicrobial preparations other than antibiotics also. Particularly, *in vitro* the bacterial isolate demonstrated good susceptibility to the "Stomatidin", "Chlorophyllipt", and "Pyofag" (Table 3). The "Decatylen", "Decasan" and "Furadonin" were less effective *in vitro*. They produced small inhibition zones (less than 10 mm in diameter). The "*Pelargonium sidoides* roots extract Eps® 7630", a

Table 3. Sensitivity of *Streptococcus pyogenes* BS1 in vitro to antimicrobial agents other than antibiotics

Antimicrobial agent	Applied disc content	Mean inhibition zones in bacterial lawns, mm
Stomatidin (clorhexidin) (hexetidin 0.1% solution)	20 μg	35
Decatylen lozenges (0.25 mg dequalinium chloride/0.03 mg cinchocaine hydrochloride)	25 μg/3 μg	8
Decasan (0.02% decamethoxine solution inhalation antiseptic)	20 μg	5
Furadonin (nitrofurantoin)	20 μg	9
Chlorophyllipt	20 μg	26
A prodelphinidin-rich ethanolic extract (1:9-11), from *Pelargonium sidoides* roots DC, EPs® 7630	20 μL	No zone
Calendulae flos (*Calendula* flowers extract in 70% ethanol, 1:10)	20 μL	No zone
"Pyofag", the phages suspension	20 μL	33

drug for treatment of respiratory tract infections and "Calendulae flos" the *Calendula* flowers extract in 70% ethanol, 1:10 (LLC DKP Pharmaceutical factory, Ukraine) was not active in *Streptococcus pyogenes* BS1 lawns (Table 3).

The boy's parents insisted on non-antibiotic treatment first. Thus, "Stomatidin" (hexetidine 0.1% solution) was recommended to boy to rinse the mouth and gargle with 15 ml of undiluted solution for half of minute two times a day (after breakfast and supper) and "Chlorophyllipt" was used as a spray after dinner. The treatment lasted 3 days and resulted in some decrease in body temperature (to around 37.5°C) and alleviation of pain sensations as results of size of tonsils decrease to about 62% of the oropharyngeal width, the grade +3 by [14], some decrease in redness of tonsils and surrounding area and in reduction of whitish exudation from palatine tonsils. However, symptoms were not improved on the 4th day. Particularly, neck lymph nodes and tonsils remain enlarged and body temperature still elevated (around 37.5°C).

Then, this treatment was substituted with application of the "Pyofag". The 5 mL portions of the phages suspension was administered via compressor nebulizer "Ulaizer Home" Vega Technologies Inc. (Taiwan) inhalation during 10 min after supper for 3 consequtive days. The elevated body temperature decreased further to around 37°C. The pain with swallowing was somewhat alleviated, because size of tonsils decreased more, to about 43% of the oropharyngeal width, a grade +2. However, symptoms of enlarged lymph nodes, the redness of the tonsils and surrounding throat areas and tonsillar exudate improved a little only.

Regarding the health state of the patient after 6 days of non-antibiotic treatment as not better enough, it was decided to treat the boy with 1 g/day of benzathine phenoxymethylpenicillin in preparation OSPEN® ("Biochemie GmbH", Germany) administered orally as water suspension in four 5 mL spoons each containing 250 mg (400000 IU) of the antibiotic with interval intake of 6 hours. Additionally, as an anti-inflammation treatment, one teaspoon of *Calendula* flower extract was diluted in 150 ml of warm boiled water and used for rinsing of the throat. This was done 4 times per day after the antibiotic intake. The health of the boy significantly improved on day 4th of the antibiotic and *Calendula* extract use. Particularly, body temperature normalized, tonsillar exudation ceased completely. The redness of the tonsils and surrounding throat areas decreased further. The boy received this treatment for the 6 following days to fulfill the WHO's recommendation of 10 days for longevity of the antibiotic use. On day 7 of such a therapy the redness of the tonsils and surrounding throat areas almost completely disappeared and tonsils and neck nodes significantly decreased in size. Particularly, tonsils decreased in size to the grade +1 (they were just outside of the tonsillar fossa and occupied about 20% of the oropharyngeal width).

The blood analysis following treatment demonstrated 37% of lymphocytes among leukocytes (Table 1). Thus, the lymphocytes decreased in number to normal levels for adults.

Regarding the reports about development of reduced susceptibility to β-lactams resistance to other antibiotics of choice, such as clindamycin and macrolides in *Streptococcus pyogenes* [4, 5, 18, 19], the negative effect on microbiome of patients [20] and possible complications in patient's organism after the antibiotics use [22, 23], parents together with doctors have the right to decide whether to use these antimicrobials for their children treatment or not.

The parents of the boy insisted on non-antibiotic therapy first. We started it with "Stomatidin" and "Chlorophyllipt". They provided only partial alleviation of symptoms.

The "Stomatidin" is an antiseptic agent for topical use, particularly during streptococcal pharyngitis [24]. Its weak analgesic effect explains some pain relief in a boy's throat with swallowing at the start of his treatment. It has non-specific antimicrobial action and must be used with care not to affect the normal flora of the throat. Its application was intermitted with "Chlorophyllipt" spray. Together these preparations provided some improvement in the patient's health.

The "Decatylen", "Decasan" and "Furadonin" we not used in treatment, because they were less effective on *S. pyogenes* BS1 lawns, than "Stomatidin" and "Chlorophyllipt" prepared discs or "Pyofag".

The dequalinium chloride was reported as effective in curing of sore throat infection [6, 25]. However, in our case this and other quaternary ammonium compound, the decamethoxine, were not chosen as the treatment, because of their lower activity against *Streptococcus pyogenes* BS1 *in vitro*, compared to stomatidin, chlorophyllipt or bacteriophage (Table 3). Recently, Sydorchuk et al. [26] reported the decrease in sensitivity to decamethoxine over 50 years of its use by 5.42-3.63 times in clinical strains of *S. pyogenes*.

Earlier Kayser O. and Kolodziej H. [27] demonstrated antibacterial activity of extracts and constituents of *Pelargonium sidoides* and *Pelargonium reniforme* against β-hemolytic streptococci. However, in our case study, a prodelphinidin-rich ethanolic extract (1:9-11) from *Pelargonium sidoides* roots DC, EPs® 7630, was inactive against *Streptococcus pyogenes* BS1 in Petri dishes. Earlier Uslu H. and co-workers [28] reported about resistance of *Streptococcus pyogenes* to this plant extract also. The *Calendula* flowers extract has no antimicrobial action against our *S. pyogenes* isolate. The extract was used as a gargle to decrease local inflammation. The "*Calendulae flos",* a *Calendula* flowers extract, was inactive against *Streptococcus pyogenes in vitro*, however, demonstrated good anti-inflammatory properties, when applied in time between benzathine phenoxymethylpenicillin intakes. The extract was approved [29] as an anti-inflammatory agent for the throat. Possibly, this herbal preparation can have more wide use in strep throat treatment.

The "Pyofag" suspension contains phages that kill *S. pyogenes* and produce a large zone of cell lysis in the *Streptococcus pyogenes* BS1 lawn. However, few colonies were growing in such zones, the evidence that some streptococcal cells were resistant to the phage. The application of phages resulted in somewhat alleviated symptoms within 2 days, but symptoms not demonstrated further decrease on day 3rd of phage inhalation. This suggests that some cells of streptococci in patient were resistant to the phage or phage particles had no access to the part of the bacterium cells, possibly, to those, present in tonsillar crypts and harboring in other anatomical gaps or in depressions of the tissues as the films. Thus, phage was unable to attack all cells of *Streptococcus pyogenes* in the throat of the boy. Enlarged lymph nodes, the redness of the tonsils and surrounding throat areas and tonsillar exudate presence suggested that some bacteria were protected from the phage by human organism relief or able to resist phage action.

The benzathine phenoxymethylpenicillin for treatment of *Streptococcus pyogenes* tonsillitis is recommended in Ukraine, particularly, by the clinical guideline approved by an extended meeting of state experts and Orders of the Ministry of Health [30].

Several remedies, with different mechanisms of action onto disease agent were moderate in efficiency treatment of *Streptococcus pyogenes* tonsillitis in our case: the "Stomatidin", an antiseptic with broad antimicrobial spectrum and analgetic effect; the phages of "Pyofag" with specific action against streptococci; and "Chlorophyllipt" an antimicrobial extract from *Eucalyptus viminalis* leaves. They are, possibly, unable to provide fast recovery from the disease.

The treatments with non-antibiotic antimicrobial agents lasted for 6 days. As they were not effective enough in our patient, we then turned to antibiotic benzathine phenoxymethylpenicillin use. This antibiotic and *Calendula* extract were applied for 10 days. The complete disappearance of symptoms was observed on day 7 of antibiotic use. All together, our patient treatment lasted longer (16 days) than treatments with immediate use of antibiotics (10 days or less).

CONCLUSIONS

Thus, we used several antimicrobial preparations for this case of 'strept throat' treatment. Some non-antibiotic agents, such as "Stomatidin" and "Chlorophyllipt" or "Pyofag" manifested antimicrobial activity *in vitro* comparable to that of antibiotics. The activity *in vitro* of chosen drugs (selected by best activity *in vitro*) correlated with positive effects on patient health. However, in our case non-antibiotic remedies were less effective for fighting of streptococcal tonsillitis infection in human organism than antibiotic benzathine phenoxymethylpenicillin. The better effect of the antibiotic, possibly, is due to its better penetration into the patient tissues.

The *Streptococcus pyogenes* BS1 *in vitro* is susceptible to β-lactams, to cephalosporins and to fluoroquinolones, however, resistant to erythromycin, spiramycin, cefazolin, clindamycin, gentamicin, tetracycline, trimethoprim/sulfamethoxazole. This evidencing the resistance

spread to these antibiotics in the local *Streptococcus pyogenes* population.

Regarding possible side effects of the antibiotics use, *in vitro* active non-antibiotic preparations can be applied first for treatment of streptococcal tonsillitis. If not active enough in patients, they can be carefully substituted or supplemented by antibiotic therapy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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