



Wiadomości Lekarskie

Czasopismo Polskiego Towarzystwa Lekarskiego



Pamięci
dra Władysława
Biegańskiego

TOM LXXI, 2018, Nr1 cz II

Rok założenia 1928

Wiadomości Lekarskie is abstracted and indexed in: PubMed/Medline, EBSCO, SCOPUS, Index Copernicus, Polish Medical Library (GBL), Polish Ministry of Science and Higher Education.

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PRACE ORYGINALNE
ORIGINAL ARTICLES

THE EVALUATION OF TEETH LOOSENING OF THE UPPER JAW IN ADAPTIVE PERIOD OF ORTHODONTIC TREATMENT BY BRACES

OCENA ROZLUŻNIENIA UKŁADU ZĘBOWEGO SZCZĘKI W OKRESIE ADAPTACYJNYM LECZENIA PRZY POMOCY APARATU ORTODONTYCZNEGO

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ABSTRACT

Introduction: Tooth loosening is divided into physiological and pathological one, but there is tooth loosening that occurs during orthodontic treatment (OT) and depends on the tissues of parodontium and strength of orthodontic apparatus.

The aim of the research is to evaluate teeth loosening of the upper jaw during adaptive period in patients with permanent bite who were treated by braces.

Materials and methods: Periostometry (device «Periotest») of teeth to 30 patients who are from 14 to 27 years old with the pathology of the first type based Angle's classification. The evaluation of teeth loosening was done before OT, in 1 month, in 3 months and in 6 months.

Results: The average index of teeth loosening before OT in patients included $3,08 \pm 1,29$, so it corresponded to norm indices. In 1 month after braces fixation indices of tooth loosening were increased. Middle index of teeth loosening on the third month of OT was $5,84 \pm 0,77$ relative units, that in 1,9 times more than periostometric indices before OT.

Conclusions: Changes of teeth loosening during OT by braces during the first month after fixation. It should be noted that during the first month of OT data of periostometry determine the enlargement of teeth loosening of all teeth in 1,38, in 3 months there is decrease of teeth loosening for all types of teeth. On the 6th month of OT indices of teeth loosening continue decreasing but with lesser intensity and not achieve such level which was to the beginning of OT.

KEY WORDS: orthodontic treatment, adaptation, periostometry, "Periotest"

Wiad Lek 2018, 71, 1 cz. II, 123-127

INTRODUCTION

Tooth loosening is divided into physiological and pathological one, but there is tooth loosening that occurs during orthodontic treatment (OT) and depends on the tissues of parodontium and strength of orthodontic apparatus.

In dental clinic there are such types of diagnostic treatment as electroodontodiagnostics, gnathodynamometry, reoparodontography, periostometry [1, 2, 3].

Periostometry is the evaluation of supporting tissues of tooth and their functional possibilities by the device «Periotest» [4], which is widely used in dentistry and measures the reaction of parodontium by microcomputer tooth percussion [5, 6, 7]. Results of periostometry determine the condition of parodontium health which is biophysical volume such as blood pressure [8], that is why this type of evaluation of tooth loosening is very important and objective index of loss of bone mass of parodontium [6, 8]. This comparatively new method is used to diagnose periodontal diseases, to measure physiological tooth loosening, to evaluate periodontal tissues during orthodontic treatment, to determine primary stability of orthodontic mini-implants and also to define osteointegration of dental implants [9, 10, 11, 12, 13, 14, 15].

Periotest demonstrates high stage of accuracy, responsibility and repetition [5, 17]. English scientists determined that due to periostometry there are more abnormalities of periodontal tissues than due to modern methods [9].

Measurements of the device «Periotest» are characterized by accuracy and depend on tooth loosening so they depend on peculiarities damping of parodontium, age and sex of the patient [16, 17], length, number and stage of root resorption [13], that is determined by dental inclination [10, 12, 18]. At healthy parodontium indices of tooth loosening are stable and do not have differences between left and right sides [7, 16], but with age they can decrease [17].

During retentional period of orthodontic treatment the tendency of tooth loosening continues 12 months [7, 19], but it doesn't approach to initial indices, that's why Tanaka E. recommends using Periotest to determine individual terms of retentional period [3, 12], but frontal teeth loosening depend on type of the replacement of middle line [20].

At orthodontic treatment by removable dental plate teeth loosening increases during its activation, but tendency to decrease occurs after in only three weeks [21], that is scientifically manifested term for the next activation of removable apparatus.

«Periotest» is the device to determine changes of teeth loosening during different stages of orthodontic treatment. Teeth loosening during orthodontic treatment (OT) define pain sensations and discomfort in patients. M.S. Drohomiyetska considers that maximal teeth loosening occur on the 4th-6th months of OT [22].

It has been proved that one of the cause of treatment interreption is patient's adaptation to orthodontic apparatus. But these factors have not studied yet [23].

Table I. Indices of the level of teeth loosening based on Gulden

Level of teeth loosening	Indices Periotest
norm	- 08 - +09
I	- 10 - +19
II	- 20 - +29
III	- 30 - +50

Table II. Dynamics of changes of average indices of tooth loosening of the upper jaw in patients during 6 months of OT (in relative units)

Teeth Measurement term	16	15	14	13	12	11	21	22	23	24	25	26	Average indices of all teeth
Before OT	1,83 ± 1,29	3,92 ± 1,27	3,33 ± 1,72	1,42 ± 1,29	4,25 ± 1,80	3,75 ± 2,29	4,17 ± 2,96	4,08 ± 1,86	1,33 ± 1,18	3,09 ± 1,97	3,58 ± 1,86	2,17 ± 1,70	3,08 ± 1,29
In 1 month	2,52 ± 1,26	7,29 ± 1,70	6,14 ± 1,46	4,77 ± 1,73	8,24 ± 3,50	9,23 ± 1,80	10,41 ± 3,16	8,99 ± 2,64	5,30 ± 3,99	7,00 ± 2,80	8,24 ± 3,03	4,29 ± 2,29	6,87 ± 1,76
Difference in 1 month	1,38**	1,86*	1,84*	3,37*	1,94*	2,46*	2,50*	2,20*	3,97*	2,26*	2,30*	1,98*	2,23*
In 3 months	2,99 ± 1,07	6,29 ± 1,04	7,01 ± 1,04	3,95 ± 0,88	7,18 ± 1,27	8,10 ± 1,22	7,12 ± 0,93	5,98 ± 1,40	3,61 ± 0,54	7,20 ± 1,51	7,14 ± 2,15	3,58 ± 0,97	5,84 ± 0,77
Difference in 3 months	1,63*	1,60*	2,11*	2,79*	1,69*	2,16*	1,71*	1,46*	2,71*	2,33*	1,99*	1,65*	1,90*
In 6 months	2,00 ± 0,71	7,25 ± 1,79	6,25 ± 1,30	3,25 ± 1,64	7,50 ± 1,12	8,50 ± 1,12	8,51 ± 1,56	6,75 ± 1,79	2,75 ± 0,83	4,50 ± 1,80	8,00 ± 4,36	2,24 ± 0,57	5,60 ± 0,74
Difference in 6 months	1,09**	1,85*	1,88*	2,29*	1,76*	2,27*	2,04*	1,65*	2,07*	1,46**	2,23**	1,03**	1,83*

* - statistically accurate
 ** - statistically inaccurate

THE AIM

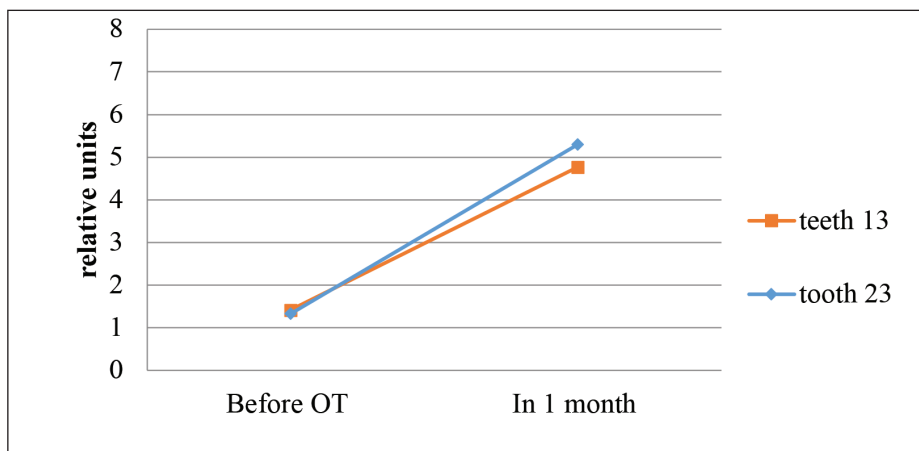
The aim of the research is to evaluate teeth loosening of the upper jaw during adaptive period in patients with permanent bite who were treated by braces.

MATERIALS AND METHODS

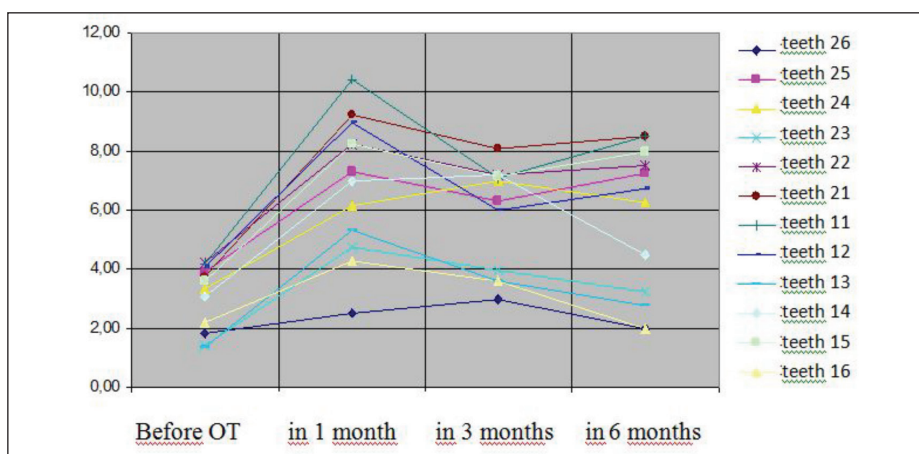
Periostometry (device «Periotest») of teeth of the upper jaw to 30 patients who are from 14 to 27 years old with the pathology of the first type based Angle’s classification without concomitant diseases was done. The evaluation of teeth loosening was done before OT (10 patients), in

1 month (7 patients), in 3 months (7 patients) and in 6 months (6 patients). Patients were treated by similar fixed orthodontic apparatus (braces), sequence of arches was similar: 0,012 NiTi, 0,014 NiTi, 0,016 NiTi. 360 measurements were done.

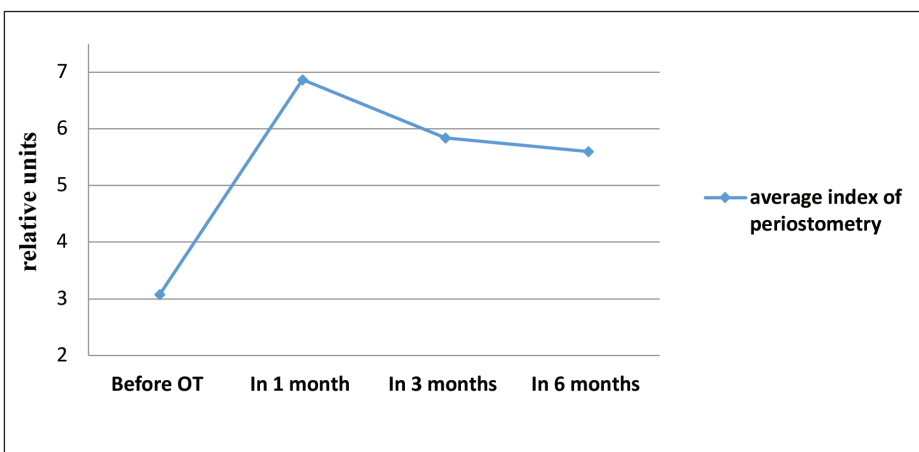
Periotest – is modern electromechanical device of Germany (Gulden) production to determine damped peculiarities of periodontal tissues [10, 11, 20]. The working element of the device is adapter with piezoelectric element, the frequency of mechanical impulses contains 4 ranges per 1 sec., and duration of all cycle for each tooth – 4 sec. or 16 impulses.



Picture 1. Diagram of tooth loosening of the 13th and the 23d teeth in 1 month of OT



Picture 2. Dynamics of teeth loosening of the upper jaw during OT



Picture 3. Dynamics of average index of teeth loosening of the upper jaw during 6 months during OT

Healthy periodontal tissues have more flexible peculiarities in comparison with tissues that were affected by pathological factors or orthodontic treatment. Damping of mechanical ranges from Periotest in healthy tissues occurs quicker than during pathology, that's why this difference [17] uses Periotest-method to evaluate reformation of bone mass [3].

Clinically Periotest indices correspond to the stage of teeth loosening and the limit of measurements is from -08 to +50 relative units. The lesser index for each tooth was defined, periodontal tissues are in the better condition (table I). Inaccuracy during recurrent measurements for

each tooth in each period of time doesn't exceed ± 1 relative units, and it can coincide with such measurements [5].

Percussion was done according to the instruction between contour and tooth cutting edge, patient's head was slightly inclined downwards during the investigation of upper frontal teeth.

RESULTS

The average index of teeth loosening of the upper jaw before orthodontic treatment in patients with permanent

bite was from $1,33 \pm 1,18$ to $4,25 \pm 1,8$ relative units and on average included $3,08 \pm 1,29$, so it corresponded to norm indices (table II).

The least tooth loosening was observed in canines both right ($1,42 \pm 1,29$) and left ($1,33 \pm 1,48$) and it is associated with root length. The second part of tooth loosening included the first molars from both sides (1, 83 – 2,17), the next one – the first premolars (3,09–3,33). Indices of incisors and the second premolars loosening were the largest but they differed depending on the side: from the right side the largest lateral incisors loosening was the biggest one ($4,25 \pm 1,80$ relative units), and from the left one the biggest index in the central incisors was observed ($4,17 \pm 2,96$ relative units, on 0,59 relative units). There is not statistically difference between indices of the right and the left sides and it coincides with scientific information [12, 16].

In 1 month after braces fixation indices of tooth loosening of the upper jaw were increased. Before orthodontic treatment average indices of teeth loosening included $3,08 \pm 1,29$ relative units, and in 1 month they increased with statistically accuracy in 2,23 times and indices included $6,87 \pm 1,76$ relative units (table II).

The biggest influence of teeth loosening before OT was observed in frontal group of teeth. So, tooth loosening increased on the 13th and the 23^d teeth in 3,37 times in 3,97 times correspondingly (table I). In general from the left side dynamics of teeth loosening of the upper jaw is higher than from the right one.

Middle index of teeth loosening of the upper jaw on the third month of OT was $5,84 \pm 0,77$ relative units, that in 1,9 times more than periostometric indices before orthodontic treatment. The biggest increase of indices of teeth loosening was observed in the frontal part of teeth: incisors of both right ($8,10 \pm 1,22$ relative units) and left sides ($7,12 \pm 0,93$ relative units) and canines (table II). But, comparing indices in 1 month of orthodontic treatment with indices in 3 months one can see frontal teeth loosening, the second premolars and the left first molar decrease and indices of the first premolars of both sides and the right first molar increase. Average indices of teeth loosening on the third month in comparison with indices of the first month of OT decreased in 1,03 relative units (table II). Dynamics of teeth loosening from the left side decreases and from the right one increases.

In 6 months after orthodontic device fixation, indices of teeth loosening were observed in the frontal group of teeth: both in canines on the right side and on the left one increased in 2,29 and in 2,07 correspondingly, and in central incisors in 2,27 and in 2,04 times correspondingly. But the biggest index of tooth loosening was observed in central incisors and included 8,5 relative units, that increased in 2 times, than before OT.

Index of the first molars loosening approaches to indices before OT and include correspondingly 2,0 and 2,24 relative units (from the left and the right sides), that on 0,17 units and on 0,07 units is lesser than at the beginning of orthodontic treatment. During 6 months of OT the first premolars, the first molars and canines loosening decreases and loosening of the second premolars and incisors starts

increasing in comparison with results in 3 months from the beginning of OT (table II).

In general analysis of dynamics of changes of average indices demonstrates that the most increase of periostometry is observed during the first month from the beginning of treatment that coincides with clinical signs in patients: pain in teeth, discomfort and others and it doesn't coincide with information based on M.S. Drohomyretska who determined maximal loosening on 4–6 months of OT. During the next 5 months indices of teeth loosening decrease, clinical signs in most cases disappeared and in general periostometric indices do not approach to indices before OT (picture 2).

Changes of teeth loosening of the upper jaw during OT by braces during 6 months have the next tendency: during the first month frontal teeth loosening increase, in 3 months loosening of frontal teeth reduces, but loosening of masticatory teeth continues increasing, besides the 15th and the 25th teeth, and periostometric indices decrease. In 6 months of orthodontic treatment loosening of such teeth as 11, 12, 21, 22, 15 and 25 increases and loosening of such teeth as 13, 23, 14, 24, 16 and 26 decreases, and it doesn't coincide with the level which was present before OT (picture 2).

CONCLUSIONS

So, changes of teeth loosening of the upper jaw during orthodontic treatment by braces in adults occur during the first month after fixation that is determined as the period of discomfort, tooth pain, and it is coincided with adaptation to fixed and can cause patient's refusal from further OT. It should be noted that during the first month of OT data of periostometry determine the enlargement of teeth loosening of all teeth in 1,38 (Picture 3), in 3 months there is decrease of teeth loosening for all types of teeth.

On the 6th month of OT indices of teeth loosening continue decreasing but with lesser intensity and not achieve such level which was to the beginning of orthodontic treatment.

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Received: 20.09.2017**Accepted:** 12.01.2018

EFFECT OF PROLONGED AND INTERMITTENT TREATMENT ON THE CLINICAL COURSE OF PEPTIC ULCER

SKUTECZNOŚĆ PRZEDŁUŻONEGO I OKRESOWEGO LECZENIA NA KLINICZNY PRZEBIEG OWRZODZENIA ŻOŁĄDKA

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ABSTRACT

Introduction: The number of patients with peptic ulcer increases annually. According to published data, patients with peptic ulcer constitute about 15% of those hospitalized with gastrointestinal diseases.

The aim: That is why we set the task to evaluate the methods of preventive treatment and to choose the most effective one.

Materials and methods: For this purpose, we selected 103 patients with peptic ulcer without severe exacerbations and complications from one region (main group) and 101 patients from another region (control group) for observations. Making diagnosis was based on the study of complaints, anamnestic data, physical examination of the patient, evaluation of the functional state of the gastroduodenal system, as well as the X-ray and endoscopic examination. The sources of the study were medical records of outpatients, control cards for dispensary surveillance, registers of temporary disability records, sick leave records and others.

Results: Most patients, from both the main and control groups, who were on prophylactic treatment, noticed that they had an increased working capacity, normalized sleep, better appetite and fewer dyspeptic disorders. Patients in the main group for two years were on prolonged prophylactic treatment according to the method that we had developed. by us. Patients in the control group received an intermittent preventive treatment twice a year (in spring and autumn). In the complex of therapeutic measures the following were used: dietary recommendations, antacids, cholinolytics, multivitamins, etc.

Conclusions: Prolonged prophylactic treatment is an effective means to combat exacerbations and complications of peptic ulcer and can be recommended for implementation in practice.

KEY WORDS: peptic ulcer, prolonged prophylactic treatment, intermittent preventive treatment, diet, corrections of the treatment

Wiad Lek 2018, 71, 1 cz. II, 128-134

INTRODUCTION

One of the most important tasks of modern medicine is still the development of measures to prevent the disease of the gastrointestinal tract (GIT). Particular attention is required for gastric and duodenal ulcers.

According to the traditional definition of the World Health Organization (WHO), peptic ulcer (ulcus ventriculi et duodeni-pepticum, morbus ulcerosus) is a common chronic relapsing disease, inclined to progression, with a polycyclic course, the characteristic features of which are seasonal exacerbations, which are accompanied by the ulcer defect in the mucous membrane, and the development of complications that threaten the life of the patient. [1] The peculiarity of the course of gastric ulcer is the involvement of other organs of the digestive apparatus in the pathological process, requiring timely diagnosis to develop therapeutic complexes for patients with peptic ulcer, taking into account concomitant diseases. Gastric ulcer affects people of the most active, able-bodied age, causing temporary, and sometimes, permanent loss of ability to work [2]. High morbidity, frequent relapses, prolonged disability of patients, resulting in significant economic losses - all this makes the problem of peptic ulcer one of the most urgent in modern medicine.

A great number of papers is devoted to the study of ulcer disease. However, many issues of etiology, pathogenesis, epidemiology, and especially the issues of prophylactic treatment of peptic ulcer are still not enough developed and do not fully meet the needs of practical medicine [3].

It is the prophylaxis which takes a special place in the treatment of patients with peptic ulcer.

Peptic ulcer is a disease with prolonged chronic course, frequent exacerbations and complications. Due to the complications, about 14% of patients become 2nd group disabled people and 37% become handicapped people of the third group.

That is why finding out the causes of relapse and complications of peptic ulcer and developing measures aimed at their prevention is one of the most pressing problems of modern medicine.

Many researchers believe that inadequate treatment in hospital is the initial cause of gastric ulcer relapses, almost 47% of patients are discharged from hospital without improvement [4].

A great role is also played by mental overstrain, neurohumoral imbalance, trophic disruption and activation of proteolysis of the gastric mucosa, and often the presence of helicobacter pylori infection, as well as by alcohol and tobacco abuse [3].

Table I. Distribution of patients of the main group by age, sex, variant of the course of the disease and its duration presented

Peptic ulcer (variants of its course)	The number of patients	%	Age								Duration of disease (years)			
			adolescent		adult				elderly		1-5	5-10	10-15	15 and more
			years		1 period years		2 period years		years					
			17-21	16-20	22-35	21-35	36-59	36-55	60-74					
			Sex								1-5	5-10	10-15	15 and more
m	f	m	f	m	f	m	f							
Chronic gastritis (ulcerative variant)	18	17,5	3	1	7	2	4	1	-	-	7	11	-	-
Duodenal or/and pyloric ulcer (typical variant)	56	54,4	-	-	21	8	19	7	3	-	15	37	4	-
Gastric ulcer	29	28,1	-	-	9	5	11	4	-	-	8	19	2	-
Total	103		3	1	37	15	34	12	3	-	30	67	6	-

Table II. Distribution of patients of the control group by age, sex, variant of the course of the disease and its duration presented

Peptic ulcer (variants of its course)	The number of patients	%	Age								Duration of disease (years)			
			adolescent		adult				elderly		1-5	5-10	10-15	15 and more
			years		1 period years		2 period years		years					
			17-21	16-20	22-35	21-35	36-59	36-55	60-74					
			Sex								1-5	5-10	10-15	15 and more
m	f	m	f	m	f	m	f							
Chronic gastritis (ulcerative variant)	14	13,9	1	1	7	2	2	1	-	-	5	9	-	-
Duodenal or/ and pyloric ulcer (typical variant)	61	60,4	2	-	19	6	28	6	-	-	16	40	4	-
Gastric ulcer	26	25,7	-	-	6	4	13	2	1	-	9	16	1	-
Total	101		3	1	32	12	43	9	1	-	30	65	5	-

Diet is particularly important in preventive treatment. Appropriately organized, rationally differentiated medical nutrition is an indispensable way of preventing recurrent peptic ulcer.

In recent years such methods of treatment as vitamin therapy, therapeutic physical training (TPT), acupuncture, pressure point massage, physiotherapy, drinking mineral waters, balneotherapy, music therapy, mud therapy and phytotherapy have become very popular [5].

However, the unsystematic use of various means to combat relapse of peptic ulcer does not always lead to the desired effect and may even have a reverse effect resulting in the aggravation of health [6].

THE AIM

To evaluate the methods of prophylactic treatment of peptic ulcer used, to compare them and develop the most effective technique for prolonged prophylactic treatment.

MATERIALS AND METHODS

In order to achieve our goals we registered 103 patients with ulcer disease without severe exacerbations and complications in five settlements of Chernivtsi region for prolonged preventive treatment. As a control group, 101 patients with peptic ulcer without severe exacerbations and complications were selected in five settlements of Ivano-Frankivsk region, which remained on preventive treatment with breaks.

Table III. Data on the clinical and functional status of patients with peptic ulcer before the transition to prolonged prophylactic treatment and preventive treatment with breaks are given

Complaints	Number of patients			
	Main group		Control group	
	Abs. number	%	Abs. number	%
Slight sensation of heaviness in the epigastric area	39	37,8	46	45,5
Short-term pain in the epigastric area	26	25,2	30	29,7
Periodic heartburn	21	20,4	23	22,7
Periodic eructation	26	25,2	25	24,7
Constipation	27	26,2	24	23,8

Table IV. Distribution of patients according to the rates of the functional state of the stomach (before treatment) presented.

Functional rates of the stomach	Lowered		Within the normal range.		Heightened	
	Main gr.	Control gr.	Main gr.	Control gr.	Main gr.	Control gr.
Gastric juice on an empty stomach	13	15	28	32	62	54
Gastric juice under time pressure	8	10	35	33	60	53
The hydrochloric acid content on an empty stomach	11	8	31	27	61	66
hydrochloric acid discharge	7	12	44	41	52	48
Pepsin content on an empty stomach	17	14	29	34	67	53
pepsin discharge under time pressure	16	19	36	33	52	49
Intra-gastric pH monitoring	65	60	26	24	12	17

Making the diagnosis was based on the study of complaints, anamnestic data, physical examination of the patient, evaluation of the functional state of the gastro-duodenal system, as well as the X-ray and endoscopic examination. Inclusion criteria [7]: patients were included in the study group after their informed consent with a verified diagnosis of gastric ulcer.

Distribution of patients of the main group by age, sex, variant of the course of the disease and its duration presented in the table I. Distribution of patients of the control group by age, sex, variant of the course of the disease and its duration presented in the table II.

According to the data provided, the main and control groups of patients with ulcer disease were approximately the same by age, sex, variant of the course of the disease and its duration.

In both the main and control groups, a larger proportion of patients was observed in adulthood, the share of teenagers was 4.12% and 4.04%, and that of elderly people constituted 3.09% and 1.01% respectively. The duration of the disease in most of the patients was from 5 to 10 years.

Data on the clinical and functional status of patients with peptic ulcer before the transition to prolonged prophylactic treatment and preventive treatment with breaks are given below (table III). According to the objective data, minor pain in the epigastric region was observed in palpation in 24 (23.3%) patients of the main group and 19 (18.8%) individuals of the control group. During the laboratory examination of blood and urine, the rates were within the

normal range. Distribution of patients according to the rates of the functional state of the stomach (before treatment) presented in the table IV.

In order to clarify the diagnosis, 15 patients from the main group and 12 from the control group underwent fibrogastroscopic examination.

Patients in the main group for two years were on prolonged prophylactic treatment according to the method that we had developed by us.

The prophylactic treatment of patients in the remission period started at home: the patients in the stage of exacerbation were hospitalized and their prophylactic treatment started after their discharge from hospital.

Medical nutrition was considered to be very important in the prolonged prophylactic treatment.

Diet №1 with enough protein, fats and carbohydrates was prescribed in the first 2 - 3 months after exacerbation. Patients with severe pain syndrome (in anamnesis) were given a glass of fat milk at night (neutralizes hydrochloric acid, reduces the peristalsis of the stomach). Before switching to a normal diet, it was recommended to include diet № 5 with stress zigzag. As a source of fat-soluble vitamins, it is possible to use olive or sunflower oil. The patients were recommended medium-timed eggs, soup of cereals, vegetables (except cabbage), milk soup with spaghetti or noodles. They also were administered vegetables, greenery, fruit and berries. The patients took broth from wheat bran (sources of vitamin B1). Particular attention was paid to the proper culinary processing of food (cleaned vegetables should not stay sliced for a long time).

Of particular importance was the use of potato and cabbage juice. Without peeling them, raw potatoes are washed, wiped and squeezed through a gauze. Fresh potato juice is consumed before meals 2 - 3 times a day 0.25 - 0.5 cups for 10 - 15 days.

Cabbage juice was recommended to patients with reduced secretory activity 0.5 cups 2 to 3 times daily before meals for 10 to 15 days. In the case of individual intolerance to juices, their use for treatment was canceled.

When prescribing a medical treatment it is necessary to remember about the possible occurrence of a medical illness. Sedation agents and cholinolytics were administered strictly for 2 - 3 weeks. When appointing antacids it should be taken into account that calcium alkali are recommended for high acidity of the gastric contents and diarrhea while the magnesium ones are prescribed in case of propensity to constipation.

Medicinal herbs, some of which were prescribed as oxygen cocktails were widely used for therapeutic purposes. The therapeutic effectiveness of medicinal plants is due to the content of various active substances (alkaloids, glycosides, polysaccharides, essential oils, organic acids, antibiotics, vitamins, trace elements, tannins, amino acids, resins, fatty oils). These substances are successfully used to treat and prevent diseases of the gastrointestinal tract. Oxygen drink is a herbal potion saturated with oxygen. An oxygen drink, was prepared with infusion of the sweet flag root, of St. John's wort, milfoil, motherwort, marsh cudweed, wild rose, chamomile. For the foam formation and taste, chicken egg white and currant syrup, cherries and strawberries were added.

Mineral bottled water was used. Preference was given to poorly mineralized alkaline waters (Borjomi, Bukovyna, Luzhanska, Polyana-Kvasova, Svaliava). At considerable mineralization, water was diluted with boiled water. The course of treatment began with a single dose of 0.25 cups of water, gradually increasing to 100 - 200 ml.

Taking into account the patient's age, sex, working conditions and everyday life, therapeutic physical training was used. Young people were allowed to do sports in the period of stable remission.

When peptic ulcer was accompanied by weight loss, multi-caloric vitaminized food was recommended. Lipotropic substance and limited physiotherapy procedures were administered for the elderly.

Schemes of prolonged prophylactic treatment for each patient were individual, taking into account the peculiarities of the clinical course of the disease, as well as the effectiveness of the therapy.

The account of the months mentioned in the scheme attached does not correspond to the calendar ones, the account of months starts from the moment of relapse elimination.

Patients were admitted to the gastroenterological department of the central district hospital for periodic treatment. Both the patients in the stage of exacerbation and those who needed some prophylaxis were sent to hospital.

Much attention was paid to monitoring the progress

of individual prophylactic treatment. For this purpose, we developed and printed a special scheme of prolonged preventive treatment which was enclosed in the outpatient card of each patient (f. 025 / o), who was under the dispensary observation for peptic ulcer. When visiting the patients, we made some corrections in this scheme if it was necessary and their treatment became individual.

If the patients did not come at the appointed time, district nurses made an active call to them and, if necessary, visited them at home. All patients who were on prolonged prophylactic treatment, were systematically examined by district doctors, by doctors of the gastrointestinal office in due time. During these examinations, the peculiarities of working and living conditions, family situation and other circumstances were clarified. Such conversations contributed to establishing a contact with patients, which is crucial for prolonged (anti-relapse) prophylactic therapy. Particular attention was paid to the health work of district nurses who monitored the implementation of the recommended administration by patients and timely corrections to the treatment scheme under the supervision of doctors of the gastroenterology office. Feeling a significant improvement after the treatment, patients later became more active in fulfilling all prescriptions.

The first year of preventive treatment:

The first month (after the relapse) Patients with duodenal ulcer (typical variants) were prescribed diet №1, sedative therapy (strictly according to the indications), antacids after meals at individual dosage, patients with gastric ulcer were administered diet number 1, plantain sap or plantaglugidum with food.

The second month. Patients with duodenal ulcer followed diet number 1, taking antacids after eating, patients with gastric ulcer were prescribed diet number 1, vitamins of group B (multivitamins).

The third month. Alongside with diet number 1 all the patients were prescribed food "zigzag" loading: bread of coarse grinding, "greens" (50 g finely chopped vegetables 3 times daily before meals), meat soups and cabbage soup, fried chops (of beef, chicken) fish, canned food, cheese once in 7 - 10 days; Patients with duodenal ulcer were given antacids after meals; patients with gastric ulcer were administered cholinolytics (belladonna or platyphyllinum as powders) for 2 - 3 weeks.

The fourth month. Patients with a typical variant of the disease were recommended potato juice (fresh skinny) with food against the background of an expanded diet as well as cholinolytics; patients with gastric ulcer were recommended "zigzag" unload once in 7 - 10 days and taking mineral water (warm) after eating.

The fifth month. Patients with duodenal ulcer were recommended an expanded diet with "zigzag" unload once in 7 - 10 days, drinking mineral waters before or after eating; patients with gastric ulcer - an expanded diet, bran broth, taking medicinal herbs (as infusion) with food.

The sixth month. All patients were recommended an expanded diet and prescribed electrophoresis.

Table V. Frequency of various complaints in patients with peptic ulcer before and after the treatment presented

Complaints	Number of patients							
	Primary group				Control group			
	Before treatment		After treatment		Before treatment		After treatment	
	Abs. number	%	Abs. number	%	Abs. number	%	Abs. number	%
A slight sensation of heaviness in the epigastric area	39	37,8	18	18,5	46	45,5	24	25,5
Short-term pain in the epigastric area	26	25,2	11	11,4	30	27,7	27	28,7
Periodic heartburn	21	20,4	10	10,4	23	22,7	13	13,8
Periodic eructation	26	25,2	14	14,6	25	24,7	14	14,9
constipation	27	26,2	10	10,4	24	23,8	20	21,3

Table VI. The values of the stomach functional state after the treatment presented

Functional values of the stomach	Prolonged treatment			Intermittent treatment		
	Before treatment (M±)	After treatment (M±)	p	Before treatment (M±)	After treatment (M±)	p
Gastric secretion on an empty stomach (ml)	72±1,06	57±0,9	<0,001	71±1,2	65±1,2	<0,001
Secretion time pressure secretion (ml)	116±0,2	105,6±0,24	<0,001	121,4±0,22	112,9±0,18	<0,001
Free hydrochloric acid per serving on an empty stomach (mg)	58,9±1,4	44,3±1,04	<0,001	62,5±0,15	48,3±1,4	<0,001
free hydrochloric acid debit-hour (mg)	216,1±0,5	191,4±0,5	<0,001	213,9±0,4	199,7±0,4	<0,001
content of pepsin in a serving on an empty stomach (g%)	1,2±0,03	0,77±0,02	<0,001	1,3±0,03	0,89±0,02	<0,001
pepsin debit-hour (g%)	6,6±0,2	4,6±1,15	<0,001	6,9±0,14	5,2±0,13	<0,001
Values of pH (in units)	1,53±0,04	1,92±0,05	<0,001	1,6±0,04	1,74±0,05	<0,05

The seventh month. An expanded diet and cabbage juice were given to patients with peptic ulcer disease.

The eighth month. Patients with duodenal ulcer were prescribed an expanded diet, novocaine (in solution) with food, coniferous baths. Patients with gastric ulcer were recommended an expanded diet, plantain sap.

The ninth month. Patients with duodenal ulcer received a diet, sedative therapy, antacids; patients with gastric ulcer - diet number 1, flax seeds, milfoill (in infusion) with food.

The tenth month. Patients with peptic ulcer with a typical variant of the disease were prescribed diet number 1, antacids, patients with peptic ulcer disease - diet number 1, cabbage juice.

The eleventh month. Patients with duodenal ulcer were recommended an unload against the background of the expansion of the "zigzag" diet, valerian tea; patients with gastric ulcer were given an expanded diet with an unload zigzag and vitamin tea with food.

The twelfth month. Patients with a typical variant of the peptic ulcer were on an expanded diet, they took mineral water and cholinolytics; patients with gastric ulcer were prescribed an expanded diet and mineral water.

The second year of preventive treatment:

The first month. Patients with duodenal ulcer were recommended mineral water against the background of an expanded diet; those with gastric ulcer were prescribed an expanded diet and electrophoresis.

The second month. Patients with a typical variant apart from an expanded diet were recommended flax seeds; patients with gastric ulcer were given an expanded diet and an oxygen cocktail.

The third month. Patients with a typical variant were given diet number 1, sedative therapy (according to the indications) inductothermy; patients with peptic ulcer disease were recommended diet number 1 and plantain sap.

The fourth month. Patients with a typical variant of the course of peptic ulcer were prescribed diet number 1, an unload "zigzag" and cholinolytics; patients with gastric ulcer - an expanded diet with an unload "zigzag" and coniferous baths.

The fifth month. An extended diet number 1 with an unload "zigzag" and electrophoresis were prescribed to the patients with duodenal ulcer; patients with gastric ulcer were given an expanded diet with an unload "zigzag" and coniferous baths.

The sixth month. Patients with duodenal ulcer were prescribed an expanded diet and an oxygen cocktail; patients with gastric ulcer - an expanded diet and multivitamins (especially of B group).

The seventh month. Patients with duodenal ulcer were given an expanded diet and coniferous baths, those with gastric ulcer were recommended an expanded diet and potato juice.

The eighth month. Patients with a typical variant were recommended an expanded diet and potato juice. Patients with gastric ulcer were given an expanded diet, cabbage juice and inductotherapy.

The ninth month. Patients with duodenal ulcer were prescribed diet number 1 and mineral water; patients with gastric ulcer - diet number 1 and cholinolytics.

The ninth month. Diet number 1 with an unload zigzag and antacids was given to patients with a typical variant of the disease; diet number 1 and an oxygen cocktail were prescribed to patients with gastric ulcer. of the stomach.

The eleventh month. Patients with peptic ulcer with a typical variant of the disease were prescribed an expanded diet with an unoad "zigzag" and antacids; patients with gastric ulcer - an expanded diet, an unload zigzag and mineral water.

The twelfth month. An expanded diet and an oxygen cocktail were prescribed to patients with a typical variant of peptic ulcer; An expanded diet and electrophoresis were given to patients with gastric ulcer.

RESULTS END DISCUSSION

Patients in the control group received an intermittent preventive treatment twice a year (in spring and autumn). In the complex of therapeutic measures the following were used: dietary recommendations, antacids, cholinolytics, multivitamins, etc.

Treatment of patients under the above schemes was carried out under the systematic control of the gastrointestinal consulting room and district physicians.

The majority of patients, both in the primary and control groups, who were on prophylactic treatment, noticed that they had increased working capacity, normalized sleep, improved appetite and fewer dyspeptic disorders.

Frequency of various complaints in patients with peptic ulcer before and after the treatment presented in the table V.

As can be seen from the table, the frequency of complaints of heaviness sensation in the epigastric region, eructation and heartburn in prolonged and intermittent prophylactic treatment decreased almost twice. At the same time, it should be noted that the frequency of complaints of short-term pain in the epigastric region and constipation in intermittent prophylactic treatment of patients, as compared with the baseline data, did not change much, whereas during prolonged treatment the frequency of these complaints decreased more than twice.

After the treatment, the values of the stomach functional state have also changed significantly.

The values of the stomach functional state after the treatment presented in the table VI.

As can be seen from the above findings, the values of the stomach functional state (secretory, acid forming, pepsin-forming ones) both in prolonged and intermittent treatment have improved significantly. However, it should be noted that the tendency to normalize the values of the stomach functional state in prolonged treatment is more pronounced than in the intermittent one. These differences in the trend towards normalization are statistically reliable.

X-ray examination before and after prolonged and intermittent prophylactic treatment was performed in 28 patients in the main group and 25 in the control group. In more than half of the patients, the tone of the stomach, the evacuation function and peristalsis normalized. But at the same time, the tendency to normalize the rest of the functional and morphological parameters (hypersecretion of fluid on an empty stomach, change in the relief of the mucosa, etc.) in the prolonged prophylactic treatment is much more pronounced than with intermittent one. For instance, in prolonged prophylactic treatment these values improved in almost 40% of patients, while in the intermittent one only in 18%.

For a more complete description of the displacements in the course of peptic ulcer, depending on the treatment method, we took into account and compared the incidence, complications and partial disability of the patients. The exacerbation incidence and the number of lost days with prolonged prophylactic treatment are lower than in the intermittent one. In 100 patients who were on prolonged treatment, exacerbations were observed in 9.4%, in intermittent one - in 15.2% of patients.

In total 93.7 days were lost in prolonged prophylactic treatment, and 193.3 days in the intermittent treatment. The average duration of one case was 10 and 12 days respectively.

In prolonged prophylactic treatment there were no cases of complications, while in the intermittent one there were two - bleeding and perforation.

CONCLUSIONS

During the study, the methods of using prolonged prophylactic treatment of peptic ulcer were developed and implemented, taking into account participation in the whole complex of measures. The prolonged (two-year) prophylactic treatment was carried out according to the scheme that we had proposed, and the intermittent treatment was performed according to the generally accepted scheme: elimination of social and domestic factors, administration of cholinolytics, antacids, and vitamins twice a year (in spring and autumn). After the courses of preventive treatment, the frequency of complaints of heaviness sensation in the epigastric region, eructation, heartburn with prolonged and intermittent prophylactic treatment decreased almost twice. However, the frequency of complaints of short-term pain in the epigastric region and constipation in intermittent prophylactic treatment of patients, as compared to baseline data, remained almost unchanged, while with prolonged treatment the frequency of these complaints decreased more than twice.

There were also significant differences in the secretory and acid-forming functions of the stomach in the patients who were on prolonged prophylactic treatment, gastric secretion on an empty stomach decreased from 72 to 57 ml., in the intermittent treatment from 71 to 65, secretion time pressure from 116 to 105.6 ml. respectively, free hydrochloric acid from 58.9 to 44.4 mg., and from 62.5 to 48.3 mg. respectively, free hydrochloric acid debit-hour from 216,1 to 191,4, in the intermittent treatment from 213,9 to 199,7 mg. In the study of the enzymatic function of the stomach, the content of pepsin in the portion on an empty stomach in prolonged prophylactic treatment decreased from 1.2 to 0.77g%, in the intermittent treatment from 1,3 to 0,89r%, pepsin debit-hour from 6,6 to 4,6r%, from 6,9 to 5,2r% respectively. Acid-forming function with prolonged treatment changed from 1,53 to 1,92 units, with intermittent one - from 1,6 to 1,74 units.

In X-ray examination of the GIT, there were also shifts of these functions in the direction of normalization, more pronounced in prolonged prophylactic treatment.

Therefore, it should be noted that prolonged prophylactic treatment is an effective means to combat exacerbations and complications of peptic ulcer disease.

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Received: 10.08.2017

Accepted: 05.01.2018

ВЛИЯНИЕ НАПРЯЖЕННО-ДЕФОРМАЦИОННЫХ ПРОЦЕССОВ В ЭМАЛИ ЗУБОВ НА МАРГИНАЛЬНУЮ ПРОНИЦАЕМОСТЬ РЕСТАВРАЦИЙ I КЛАССА С РАЗНЫМ ДИЗАЙНОМ КРАЯ КАРИОЗНОЙ ПОЛОСТИ

THE INFLUENCE OF STRESS-STRAIN PROCESSES IN TOOTH ENAMEL ON THE MARGINAL PERMEABILITY OF CLASS I RESTORATIONS WITH A DIFFERENT DESIGN OF THE EDGE OF THE CARIOUS CAVITY

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РЕЗЮМЕ

Введение: Из факторов, влияющих на маргинальную проницаемость реставраций в зубах, мало изучено состояние напряженно-деформационных процессов в эмали при разном дизайне края кариозной полости.

Цель этого исследования состояла в том, чтобы изучить влияние напряженно-деформационных процессов в эмали зубов на маргинальную проницаемость реставраций I класса с разным дизайном края кариозной полости.

Материалы и методы: Исследовали на 45 удаленных интактных третьих молярах, которые были разделены на три группы по 15 в каждой в зависимости от сформированных в них кариозных полостей I класса. В I группе формировали кариозную полость без скоса эмали, во II - с внешним скосом эмали, в III - с внутренним скосом эмали. Кариозные полости восстанавливали микрогибридным композиционным светоотверждаемым материалом. Зубы подвергали термоциклированию и однократной вертикальной механической нагрузке, покрывали лаком для ногтей, помещали в 1% водный раствор метиленового синего, сепарировали в медно-дистальном направлении и изучали глубину проникновения красителя. Напряженно-деформационное состояние эмали моделировали по методу конечных элементов.

Результаты: Непараметрический статистический анализ показал, что существует прямая зависимость между значениями напряжения и деформации в эмали и маргинальной проницаемостью реставраций. Чем выше эти значения, тем более глубокое проникновение красителя. При формировании края кариозной полости в виде внешнего скоса эмали наблюдается наименьшее проникновение красителя, в виде внутреннего - наибольшее. Полученные результаты могут быть полезны клиницистам при препарировании кариозных полостей I класса.

Выводы: Чем выше значения напряжения и деформации в эмали, тем больше маргинальная проницаемость реставраций. При формировании внешнего скоса эмали наблюдается наименьшее проникновение красителя, а внутреннего скоса - наибольшее.

КЛЮЧЕВЫЕ СЛОВА: кариес, напряжение и деформации эмали, препарирование кариозной полости, скос эмали, маргинальная проницаемость реставраций.

ABSTRACT

Introduction: Of the factors affecting the marginal permeability of restorations in the teeth, the state of stress-strain processes in the enamel with different design of the edge of the carious cavity has been poorly studied.

The aim of this research was to study the influence of stress-strain processes in tooth enamel on the marginal permeability of class I restorations with a different design of the edge of the carious cavity.

Materials and methods: We have examined 45 pulled out intact third molars, which were divided into three groups of 15 each, depending on class I carious cavities formed in them. In I group we formed a carious cavity without a bevel of enamel, in II - with external bevel of enamel, in III - with internal bevel of enamel. Carious cavities were restored with a microhybrid composite light curing material. The teeth were undergone thermocycling and a single vertical mechanical load, were covered with nail polish, placed in a 1% aqueous solution of methylene blue, separated in the medio-distal direction, and the depth of dye penetration was studied. The stress-strain state of the enamel was modelled by the finite elements method.

Results: Nonparametric statistical analysis showed that there is a close relationship between the values of stress and strain in enamel and the marginal permeability of restorations. The higher are these values, the deeper is the penetration of the dye. When the edge of the carious cavity is formed with external bevel of enamel, the lowest penetration of the dye is observed, with the internal bevel - the maximal. The results obtained can be useful for clinicians in the preparation of class I carious cavities.

Conclusions: The higher the values of stress and strain in enamel, the deeper the marginal permeability of restorations. When the external bevel of the enamel is formed, the dye penetrates least, and when the internal bevel is formed - the maximal.

KEY WORDS: caries, stress and strain of enamel, preparation of carious cavity, enamel bevel, marginal permeability of restorations.

ВВЕДЕНИЕ

Основной причиной недолговечности реставраций в зубах является вторичный кариес [1]. Его возникновение заставляет пациентов обращаться к стоматологу с повторными визитами для лечения одного и того же зуба, что приводит к нерациональной затрате как своего времени, так и рабочего времени врача. Результаты анкетирования врачей-стоматологов свидетельствуют, что только в 55,7% случаях они ставят пломбы по поводу первичного кариеса, в остальных – по поводу их ремонта или замены [2]. Вследствие неоднократных оперативных вмешательств на зубах снижается прочность их тканей, истончаются стенки кариозных полостей, возникают микро- и макротрещины, сколы. Поэтому вопросы долговременной сохранности пломб в зубах отражают не только медицинскую, но и социальную проблему.

Причиной возникновения вторичного кариеса зубов является несколько факторов. Ряд авторов указывают на роль физико-химических свойства восстановительного материала: его полимеризационный стресс и усадка [3, 4], качество нанесения адгезива [5]. Большое значение придают коэффициенту конфигурации кариозных полости (С-фактор) [6], технике препарирования кариозных полостей [7]. Каждый отдельно взятый фактор и их взаимное сочетание может привести к развитию вторичного кариеса [7].

В основе начального процесса развития вторичного кариеса лежит нарушение плотности краевого прилегания реставраций к тканям зуба. Среди методов индикации качества прилегания наиболее часто в публикациях упоминается оценка маргинальной проницаемости для красителя или тест на микроподтекание. Остановимся на одном из причинных факторах возникновения вторичного кариеса и рассмотрим влияние техники препарирования кариозных полостей на микроподтекание.

При оперативной обработке эмалевого края полости I класса по Блэку придерживаются двух тактических принципов: формирование скоса или его отсутствие. В настоящее время вопрос о влиянии на маргинальную проницаемость дизайна края кариозной полости остается дискуссионным, по нему в открытых публикациях существует некоторая путаница в [8].

Ряд авторов указывают, что нет необходимости делать скос вдоль краев полости [9], они приводят к ненужному увеличению полости [10]. Поэтому для реставраций I класса боковых зубов адгезивными композиционными материалами, выдвигаются отдельные требования к препарированию. Рекомендуется щадящее минимальное оперативное вмешательство без формирования скоса эмали, удаление только разрушенных тканей [11, 12, 13]. Такой подход оправдывается данными клинических исследований, которые показали, что сколы эмали при восстановлении композитами не имеют клинического значения для сохранения реставраций в течение длительного времени [14].

Некоторые считают, что маргинальная проницаемость реставраций зависит только от самого материала и его адгезивной системы. При использовании разных адгезивных системах прочность соединения материала со скошенными или несскошенными тканями зубов разная [15].

В тоже время результаты других исследований указывают на меньшее маргинальное окрашивание в полостях со скосом эмали [16].

Следует учесть, что в твердых тканях интактных зубов под влиянием функциональной нагрузки происходят естественные напряжения и деформации [17] и влияние этих процессов в эмали при разном дизайне края кариозной полости на маргинальную проницаемость реставраций мало изучено.

ЦЕЛЬ ИССЛЕДОВАНИЯ

Цель этого исследования состояла в том, чтобы изучить влияние напряженно-деформационных процессов в эмали зубов на маргинальную проницаемость реставраций I класса с разным дизайном края кариозной полости.

МАТЕРИАЛЫ И МЕТОДЫ

Проведено исследование на 45 удаленных по клиническим показаниям интактных третьих молярах, которые были разделены на три группы по 15 в каждой в зависимости от сформированных в них кариозных полостей I класса по Блэку. В I группе зубов формировали классическую кариозную полость с ровными, отвесными стенками без формирования скоса (фальца) эмали. Во II группе – делали внешний скос эмали под углом 45° к эмалево-дентинной границе. В зубах III группы полость формировали с внутренним скосом эмали.

Зубы очищали от мягких тканей, помещали в 5.25% раствор гипохлорита натрия для дезинфекции на 2 минуты и хранили в дистиллированной воде до использования. Кариозные полости формировали на окклюзионной поверхности размерами в медио-дистальном направлении 4 мм, вестибуло-оральном – 3 мм и глубиной - на 2 мм ниже эмалево-дентинной границы твердосплавным бором типа FG 700 SL из карбида вольфрама (фирма «SS WHITE») для турбинного наконечника с распылением воды и воздуха на скорости вращения 300000 об/мин.

Кариозные полости восстанавливали микрогибридным композиционным светоотверждаемым материалом LATELUX (тип II, ISO 4049:2000) (ЧП «Латус», Харьков) согласно инструкции изготовителя.

Для состаривания пломб все зубы подвергали термоциклированию в режиме 200 циклов при температуре от 5° до 55° С с экспозицией 60 секунд при каждой температуре [18]. Дополнительно на реставрацию оказывали однократную вертикальную механическую нагрузку силой 98,07 Н (соответствует 10 кг-силы) в течение 2 секунд с помощью твердомера ТР 5006-02 (НПП «ТехМаш», Россия).

Таблица I. Маргинальная проницаемость реставраций в зубах с разным дизайном края кариозной полости

Баллы	Количество зубов		
	I группа	II группа	III группа
0	5	12	3
1	9	3	5
2	1	-	5
3	-	-	2
Всего	15	15	15

Затем зубы покрывали 3 слоями лака для ногтей, не доходя 1 мм до края реставрации и вокруг нее. Образцы помещали в 1% водный раствор метиленового синего на 24 часа, промывали в проточной воде в течение 1 часа [19].

Зубы сепарировали в медио-дистальном направлении через центр реставраций алмазными дисками толщиной 0,1мм при 3000 об/мин с охлаждением. С целью устранения дефектов и грубых шероховатостей поверхность распилов полировали до зеркального блеска с помощью полировочных дисков Sof-Lex (3M ESPE).

Оценку степени проникновения красителя между реставрацией и тканями зуба проводили с помощью микроскопа Olympus BH-2 (Япония) при увеличении $\times 40$ и выражали в баллах по ISO / TS 11405- 2015 [20]: 0 – нет проникновения красителя; 1 – проникновение красителя в эмаль; 2 - проникновение красителя в дентин; 3 - проникновение красителя в пульповую камеру.

Напряженно-деформационное состояние эмали зубов изучали по ранее описанной методике [21].

Статистические данные обрабатывали на персональном компьютере с использованием пакета прикладных статистических программ Windows и Excel. Определяли среднюю (M) и ее ошибку ($\pm m$) с помощью непараметрических критериев Manna-Whitney and Wilcoxon. Различия считали значимыми с уровнем вероятности не менее 95% ($p < 0,05$).

РЕЗУЛЬТАТЫ И ИХ ОБСУЖДЕНИЕ

Распределение изучаемых образцов с разной степенью маргинальной проницаемости красителя представлено в таблице I.

В зубах, сформированных с ровными краями эмали, без скоса (I группа) проницаемость красителя составила 0.73 ± 0.15 балла. В зоне контакта реставрационного материала с разными участками края эмали в ней возникают напряжения от 220.0 до 241.5 Мпа и деформации в пределах 0.024-0.035 мм.

Во II группе зубов, в которых формировался внешний скос эмали средний бал проницаемости составил 0.20 ± 0.11 , что в 3.6 раза меньше относительно I группы ($p = 0.025$). В месте контакта с реставрационным материалом в поверхностной эмали напряжение достигает пределов 121.6-162.1 Мпа, а деформации - 0.022-0,035 мм.

При сформированном крае эмали в виде внутреннего конуса (III группа) проницаемость красителя составила 1.40 ± 0.25 балла, что в 7 раз выше ($p = 0,001$) по сравнению со II группой и в 2 раза с III ($p = 0,06$). В этих зубах в зоне контакта возникает наибольшее напряжение в поверхностной эмали – 246.1-290.9 МПа и деформации в пределах 0.028-0.035 мм в разных участках.

В процессе выполнения функции эмаль зубов подвергается внутренним напряжениям и деформациям. Это обеспечивает ей механическую прочность и способствует адаптации к функциональной нагрузке, которая передается от отдельных кристаллов гидроксиапатита эмали на всю призму, затем через дентино-эмалевую границу на подлежащие морфологические структуры. Таким путем происходит компенсация напряжений, не позволяющая разрушиться всей системе [17]. Компенсаторный механизм реализуется за счет модуля упругости отдельных эмалевых призм. На модуль упругости влияет ориентация кристаллов гидроксиапатита [22], наличие оболочки призм [23], плотность упаковки полос Гунтера Шредера в единице площади эмали [24].

Физические характеристики напряжения и деформаций в эмали интактных зубов отличаются от реставрированных. Собственное напряжение в твердых тканях интактного зуба максимально (74,2 МПа) только в области приложения нагрузки. В реставрированном зубе по поводу кариозной полости I класса максимальное напряжение значительно выше (119 МПа) и возникает в зоне контакта эмали с реставрацией [21]. Предел прочности эмали при растяжении зависит от ориентации их призм. Функциональная нагрузка, направленная по оси призм, обеспечивает 2 раза выше предел прочности эмали, чем направленная перпендикулярно к ним [25]. Эти данные свидетельствуют о важности дизайна формирования края кариозной полости I класса.

Призмы эмали в области фиссур радиально расходятся от поверхности вглубь. При препарировании эмали и формировании разного дизайна края полости они и пересекаются по-разному. Вполне очевидно, что нагрузка через реставрацию на призмы будет ориентирована не одинаково. От направления нагрузки по отношению к ним в эмали будут возникать соответствующие процессы напряжения и деформации.

В зубах, где эмалевые края кариозной полости сформированы отвесно, без скоса, призмы при препарировании пересекаются косо. Следовательно, нагрузка будет направлена частично и по оси, и перпендикулярно к ним. В зоне контакта реставрации с эмалью в ней возникают средние напряженно-деформационные процессы, в результате чего нарушается прочность соединения и микроподтекание красителя наблюдается в 10 зубах из 15 испытуемых.

При сформированном крае эмали в виде внутреннего скоса пучки эмалевых призм пересекаются вдоль оси и реставрационный материал контактирует с их боковой поверхностью. Функциональная нагрузка направлена перпендикулярно к их оси. Это наименее благоприятный вариант, при котором возникают максимальные напряженно-деформационные процессы в эмали. В 12 из 15 зубов регистрируется микроподтекание красителя, что может свидетельствовать о недостаточной плотности контакта реставрации с тканями зуба.

Наименьшие значения напряжения и деформации в эмали происходят при наличии внешнего скоса под углом 45°. При таком дизайне формировании ее края призмы пересекаются поперечно своей оси. Соответственно и нагрузка через реставрацию передается по оси призм. Это обеспечивает наиболее плотное прилегание материала к стенкам края кариозной полости и, как следствие, маргинальная проницаемость красителя наблюдается только в 3 зубах из 15.

Поскольку это исследование проведено *in vitro* его результаты можно теоретически экстраполировать в плоскость клиники. Имеются некоторые доказательства того, что тесты на микроподтекание красителя не всегда коррелируют с какими-либо клиническими параметрами (послеоперационная гиперчувствительность, маргинальное окрашивание) [26]. Молекулярная масса используемого красителя значительно меньше массы бактерий, принимающих участие в деминерализации эмали с последующим развитием вторичного кариеса. Поэтому проникновение красителя можно наблюдать в тех ситуациях, при которых бактериальные клетки проникнуть между реставрацией и краем кариозной полости не могут [27]. В связи с этим рекомендуют рассматривать полученные результаты *in vitro* как теоретический уровень максимального микроподтекания красителя, который можно ожидать в ситуациях *in vivo* [28]. Тем не менее, результаты исследования могут быть полезны клиницистам для определения тактики препарирования кариозных полостей I класса, особенно эмалевого края. Формирование внешнего скоса эмали вызывает меньшее напряжение и деформацию в ней, что приводит в минимальной маргинальной интервенции красителя.

ВЫВОДЫ

Таким образом, существует прямая зависимость между значениями напряжения и деформации в эмали и

маргинальной проницаемостью реставраций. Чем выше эти значения, тем более глубокое проникновение красителя. При формировании края кариозной полости в виде внешнего скоса эмали наблюдается наименьшее проникновение красителя, в виде внутреннего – наибольшее.

ЛИТЕРАТУРА

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Работа выполнена в рамках НИР кафедры стоматологии «Научное обоснование оптимизации и разработки методов диагностики, лечения и профилактики основных стоматологических заболеваний у населения разных возрастных групп» (№ гос. регистрации 0115U001720, научный руководитель – д. мед. н. Лахтин Ю.В.).

Авторы подтверждают, что представленные данные не содержат конфликта интересов.

Авторы выражают благодарность сотрудникам кафедры общей механики и динамики машин Сумского государственного университета за техническое консультирование при компьютерном моделировании напряженно-деформационных процессов в зубах.

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Прислана: 12.09.2017

Утверждено: 04.01.2018

THE INFLUENCE OF THE MANUAL THROMBUS ASPIRATION ON THE SHORT TERM EFFECTIVENESS OF THE PERCUTANEOUS REVASCULARIZATION IN PATIENTS WITH CORONARY ARTERY THROMBOSIS

WPŁYW MANUALNEJ TROMBEKTOMII NA KRÓTKOTERMINOWĄ SKUTECZNOŚĆ PRZEZSKÓRNEJ REWASKULARYZACJI U PACJENTÓW Z ZAKRZEPICĄ TĘTNICY WIEŃCOWEJ

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ABSTRACT

Introduction: Percutaneous coronary intervention (PCI) is one of the main issues in treatment of acute coronary syndrome with ST segment elevation (STEMI). The manual thrombus aspiration was believed to improve the results of intervention especially in patients with coronary thrombosis.

The aim: To explore the influence of manual thrombus aspiration on the short-termed prognosis after PCI in patients with STEMI and visible coronary thrombosis.

Materials and methods: 50 patients with STEMI and visible coronary thrombosis were included for exploration. Main group (MG) consists of 25 patients to whom manual thrombus aspiration was performed and comparison group (CG) of 25 patients whom were performed just conventional PCI.

Results: In the 84% patients of the MG and in 72% CG was gained TIMI 3 flow grade after the procedure ($p=0.5$). MBG 3 was reached in similar number of patients from both groups ($p=0.37$). Comparison of the ejection fraction of the LV and its' wall motion score brought the same results. The trend to better indexes of glomerular filtration rate was observed in the patients of the MG ($p=0.18$). Need of the balloon angioplasty before stenting was the unique index improved by the manual thrombus aspiration ($p=0.02$).

Conclusions: No significant advantages of the manual thrombus aspiration usage weren't revealed comparing to conventional PCI in our study in the patients with STEMI and visible coronary thrombosis. At the same time few insignificant trends were revealed. So the more powerful trial is needed to solve this problem.

KEY WORDS: percutaneous coronary intervention, acute coronary syndrome with ST segment elevation, manual thrombus aspiration, visible coronary thrombosis.

Wiad Lek 2018, 71, 1 cz. II, 140-143

INTRODUCTION

Myocardial revascularization is one of the main issues in treatment of acute coronary syndrome with ST segment elevation (STEMI). The percutaneous coronary intervention (PCI) is the most effective method of the revascularization in such patients according to the update data [1]. But the adequate perfusion can't be gained every time even after usage of last ones. The distal embolisation is the main reasons of that. It leads to the microvascular obstruction resulting in the worsening of the diseases' prognosis [2]. The microvascular obstruction causes increasing of the incidents of the early complication, negative remodeling of the left ventricle (LV), late rehospitalization caused by the heard failure and mortality [3].

It was proposed different methods for the prevention of the distal embolisation during PCI. The manual thrombus aspiration, mechanical thrombectomy and embolicprotection were the most promising of them. Recently published meta-analysis of the trials comparing effectiveness above mention methods

showed just manual thrombus aspiration to bring some advantage to ordinary PCI. Two other methods are useless or in some cases harmful [4]. Such results stimulated performance of sime trials exploring the effectiveness of the manual thrombus aspiration in patients with STEMI. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) was one of the first of them. It was single center trial. Their results showed the patients to have better myocardial blush grade (MBG) and ST segment resolution in the case of performing manual thrombus aspiration. Moreover they had significantly lower mortality, cardiac death and end point of mortality or non fatal myocardial infarction [5]. That led to the manual thrombus aspiration to gain the high II A class and B level of evidence in "The ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation" [6]. The American heart association and American college of cardiology had the same opinion on it at that time [7].

Two other large multicenter trials were performed for the investigation of the benefit of manual thrombus aspiration in the treatment of the patient with STEMI. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) was the first of them. It didn't reveal any advantages of the manual thrombus aspiration performing during PCI neither for frequency of re-infarction or stent thrombosis nor major adverse cardiac event. Furthermore the manual thrombus aspiration was ineffective in different patients' sub-groups differed by age, gender, duration, the chest pain, infarct-related coronary artery or concomitant medication [8]. The result led to downgrade of the class of evidence for the procedure from IIa to IIb in "The ESC/EACTS Guidelines on Myocardial Revascularization" published in 2014 [1].

The Trial Of routine aspiration Thrombectomy with PCI versus PCI ALone in patients with STEMI (TOTAL) was the most numerous trial exploring the effectiveness of the manual thrombus aspiration in the revascularization in STEMI patients. It didn't find any benefit of this kind of intervention over conventional PCI neither in the general population nor in the different patients' sub-groups. Moreover it was revealed significantly increased of the stroke rate in the patients after manual thrombus aspiration. Unexpectedly it occurred not only for the first 30 days but also in the period from 30 to 180 days after the disease onset (after procedure). Increasing of the stroke frequency for the first 30 days could be explained with the thrombus or air embolisation during the procedure. But increasing of it for the period from 30 to 180 days after intervention remained unexplained by the authors of the trial [9].

The American heart association and American college of cardiology were the first who reacted for the results of the TOTAL trial. They published in "2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction" the following:

Class IIb – The usefulness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI is not well established (level of evidence C)

Class III – *Routine* aspiration thrombectomy before primary PCI is not useful (level of evidence i A) [10].

But despite the *routine* manual thrombus aspiration in primary PCI isn't recommended the special sub-groups of the patients can have benefit from it. Patients with visible coronary thrombosis are possible amount them. Above mention became the reasons of our investigation.

THE AIM

To explore the influence of manual thrombus aspiration on the short-termed prognosis after PCI in patients with STEMI and visible coronary thrombosis or totally occluded infarct-related artery.

MATERIALS AND METHODS

50 patients with STEMI hospitalized in the "therapeutic window" for PCI were included for exploration. Totally occluded infarct-related artery or its' huge thrombosis were revealed in

every of them at the coronary angiography. They were divided into two groups. Main group (MG) consists of 25 patients to whom manual thrombus aspiration was performed during the conventional PCI. Comparison one (CG) consists of 25 patients whom were performed conventional PCI without manual thrombus aspiration. The patients were prescribed similar medicines according to the update guidelines. Treatments' efficacy was evaluated by the next indexes: blood flow in the infarct-related coronary by Thrombolysis In Myocardial Infarction (TIMI) grade, MBG, ST segment resolution in 60 minutes after the procedure, ejection fraction of the LV and its' wall motion score, development of the Q wave on ECG at the discharge and glomerular filtration rate in two days after the PCI. TIMI flow grade was established according the follow definition: TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion; TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory; TIMI 3 is normal flow which fills the distal coronary bed completely. Myocardial blush was defined by the criteria proposed by Van't Hof and co-authors: MBG 0, no myocardial blush or contrast density; MBG 1, minimal myocardial blush or contrast density; MBG 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and MBG 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery [12]. Good ST segment resolution was diagnosed if ST segment declined for more than 50% as compared to the baseline in 60 minutes after the PCI. The wall motion score of the LV was determined by the formula:

wall motion score = total contractility of the myocardium / 16

Total contractility of the myocardium is a sum of the points of each of the 16 segments of the LV. 1 point is given for the normal contractility, 2 – hypokinesia, 3 – akinesia and 4 – dyskinesia.

Glomerular filtration rate was calculate by means Modification of Diet in Renal Disease Study (MDRD) equation [14].

Statistical analyses of the study results were performed using the Statistica 10 (StatSoft, USA).

RESULTS

Patients from both groups didn't differ significantly according age (55.44 ± 1.45 vs. 59.04 ± 2.22 years old, $p=0.11$) and gender ($p=0.17$). Any differences weren't revealed during the frequency of the ischemic heart disease risk factors comparison between the two groups: diabetes ($p=0.67$), arterial hypertension ($p=1$), obesity ($p=1$), dyslipidemia ($p=0.59$), smoking ($p=0.77$) and frequent contact with xenobiotics ($p=1$). Thrombolysis was performed in 4 (16%) patients of the MG and 5 (20%) of the CG ($p=1$). Presentation with cardiogenic shock was twice as high in the MG vs. CG but the difference was statistically in-

Table I. Baseline characteristics of patients included in the study

	Main group n=25	Comparison group n=25	p
Age, years	55.44±1.45	59.04±2.22	0.11
Male gender,%	88	68	0.17
Diabetes, %	8	16	0.67
Arterial hypertension, %	52	56	1.0
Obesity, %	36	36	1.0
Dyslipidemia, %	40	28	0.59
Smoking, %	60	68	0.77
Frequent contact with xenobiotics, %	52	52	1.0
Thrombolysis, %	16	20	1.0
Cardiogenic shock, %	24	12	0.46
Left anterior descendents artery thrombosis, %	40	48	0.78
Multivessel disease, %	24	40	0.36
TIMI 0 before PCI, %	84	64	0.20
Time to reperfusion therapy, hour	5.48±0.62	6.32±0.78	0.43

significant ($p=0.46$). It was found in both groups similar frequency of the infarct-related lesion located in left anterior descendents artery ($p=0.78$) and of the multivessel disease ($p=0.36$) evaluating the coronary angiography data. Baseline TIMI 0 flow grade was diagnosed in nearly identical number of patients in the MG and CG ($p=0.2$). Time to reperfusion therapy, i.e. time from the symptom onset to balloon inflation (or thrombus aspiration or stenting) was similar in both groups (5.48 ± 0.62 vs. 6.32 ± 0.78 ; $p=0.43$) (Table I).

In the 21 (84%) patients of the MG and in 18 (72%) CG was gained TIMI 3 flow grade after the procedure ($p=0.5$). MBG 3 was reached in similar number of patients from both groups at the end of PCI (72% vs. 56%; $p=0.37$). Frequency of the good ST segment resolution in 60 minutes after the intervention (54% for both, $p=1$) and of the development of the Q wave on ECG (80% for both; $p=1$) were identical in MG and CG. Evaluation of the echocardiography indexes didn't show any difference in ejection fraction of the LV (48.75 ± 1.81 vs. 46.44 ± 1.68 ; $p=0.89$) and its' wall motion score (1.42 ± 0.06 vs. 1.49 ± 0.07 ; $p=0.73$) at the discharge from the hospital. The trend to better indexes of glomerular filtration rate was observed in the patients of the MG, but it didn't reach the statistical significance (76.12 ± 4.0 vs. 68.2 ± 4.59 ; $p=0.18$). Need of the balloon angioplasty before stenting was the unique index differed in both group. It was performed in 40% of patients from the MG and in 76% - from the CG ($p=0.02$).

DISCUSSION

Influence of the manual thrombus aspiration on the angiographic results of the PCI such as TIMI flow grade and MBG were researched in some trials. Significant influence of the intervention wasn't found on the frequency of TIMI 3

after the revascularization in the above mention TAPAS trial (86.0% vs. 82.5%; $p=0.12$). But it usage led to the lowering of the MBG 0-1 appearance according to the results of the last one (17.1% vs. 23.6%; $p<0.001$) [5,15]. The same result was gained in the Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention (EXPIRA). It was revealed in it the manual thrombus aspiration to increase probability of MBG 2-3 ($p=0.0001$) without influence on the TIMI 3 frequency ($p=0.9$) after the intervention [16]. The improvement of the both indexes was revealed meta-analysis of the seven randomized trials published by U.U. Tamhane and co-authors in 2010. It included 3909 patients. There was shown significant increasing of TIMI 3 flows grade ($p=0.007$) and MBG 3 ($p<0.001$) achievement in the cases of manual thrombus aspiration usage [17]. The influence of the intervention including to PCI wasn't detected on the coronary blood flow after revascularization in TOTAL and EXAMINATION trials [9, 18]. We didn't reveal improvement of both above mention indexes after the manual thrombus aspiration in our study. But it can be caused by the low patients' number. .

More successful ST-segment resolution was revealed in the most trials and meta-analysis exploring this issue in the cases of the manual thrombus aspiration usage [5,9,17]. Significant improvement of that index of efficacy wasn't find just in the EXAMINATION trial ($p=0.31$) [18]. The lower frequency of the Q wave formation on ECG at the discharge was shown after the researched procedure in the TAPAS ($p=0.001$). Even any trends weren't found in both indexes in our work.

As we already mention the ejection fraction of the LV at the discharge was compared in both groups. The difference wasn't found. The same result had been gained in the TASTE trial [8]. We couldn't find any other trials exploring this index at the same circumstance.

The lowering of need of the balloon angioplasty before stenting was revealed not only in our work but also in the EXAMINATION trial ($p < 0.001$) [18]. It can lead to the decline of the vessel wall injury.

Unfortunately we couldn't find trials to explore the influence of the manual thrombus aspiration usage on the renal function. The index can be related with contrast medium load. Moreover it can be related with the diseases course.

CONCLUSIONS

No significant advantages of the manual thrombus aspiration usage weren't revealed comparing to conventional PCI in our study in the patients with STEMI and visible coronary thrombosis or totally occluded infarct-related artery. At the same time few insignificant trends were revealed. So the more powerful trial is needed to solve this problem.

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Received: 25.08.2017

Accepted: 12.12.2017

INDICATORS OF PHAGOCYTOSIS IN WOMEN WITH ACNE DURING COMPREHENSIVE TREATMENT THAT INCLUDED IMMUNOTHERAPY AND PROBIOTICS

WSKAŹNIKI FAGOCYTOZY U KOBIET Z TRĄDZIKIEM W TRAKCIE KOMPLEKSOWEGO LECZENIA OBEJMUJĄCEGO STOSOWANIE IMMUNOTERAPII ORAZ PROBIOTYKÓW

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ABSTRACT

Introduction: Acne is one of the most common dermatological diseases. It may have a chronic course, leaving permanent marks, and in last years has been tending to have more and more severe clinical course with widespread skin lesions. According to recent studies, the development of acne is due to the combined effect of endogenous and exogenous factors, among which endocrine diseases (quite a significant aspect), disorders of metabolic processes, reduced systemic immunity and phagocytic ability of mononuclear phagocytes and granulocytes at various stages of phagocytosis of pyogenic cocci, which contributes to more severe clinical course, and frequent relapse of this diseases. It was also proved that the intestinal microbiota plays an important role in the formation of homeostasis and immune response.

The aim of the study is to determine the evolution of phagocytosis indices in patients with acne under different comprehensive treatments, using oral antibiotics, immunotherapy, probiotics and low-dose birth control pills.

Materials and methods: We observed 93 women with acne aged from 18 to 25 years old. In 19 (20,43 %) patients mild acne was diagnosed, in 41 (44,09%) – moderate acne, in 33 (35,48 %) persons – severe acne, 54 (58,06%) persons suffered from acne up to 1 year, 39 (41,93%) – from 1 to 3 years. To assess the state of phagocytosis in patients with acne vulgaris, we determined phagocytic activity (PA) and phagocytic index (PI) of polymorphonuclear leukocytes, nitro blue tetrazolium recovery test (NBT spontaneous) and NBT-test pyrogenal stimulated by the recognized methods.

Results: Analysis of the studied parameters of phagocytosis at the end of treatment showed a significant increase in patients of the core group who were administered a comprehensive treatment which included oral antibiotic, probiotic, low-dose birth control pills and autohemotherapy, as compared with the patients of other groups under study.

Conclusions: Using combined therapy for women with acne occurring against the backdrop of a sluggish process of phagocytosis and concomitant intestinal dysbiosis leads to normalization of the leading indices of phagocytosis (PI, PA, NBT tests both spontaneous and stimulated), and enhances their phagocytic activity both during capture and formation of bactericidal activity and in the final stages of phagocytosis justifying the feasibility of a combined use of antibiotics, probiotic, low-dose birth control pills and autohemotherapy in the treatment of acne.

KEY WORDS: acne, phagocytosis, probiotic, autohemotherapy, low-dose birth control pills

Wiad Lek 2018, 71, 1 cz. II, 144-147

INTRODUCTION

Acne is one of the most common dermatological diseases. It may have a chronic course, leaving permanent marks (scars, blemishes, emotional disorders), and in recent years has been tending to have more and more severe clinical course with widespread skin lesions, formation of resistance to drugs of etiotropic treatment, leading to the chronic course, decrease or loss of patient's capacity and social activity which signifies important medical and social aspects of the problem and justifies the topicality of improving treatment studies [1,2].

According to recent studies, the development of acne is due to the combined effect of endogenous and exogenous factors, among which endocrine diseases should be pointed out, as well as disorders of metabolic processes [3,4], reduced systemic immunity and phagocytic ability of mononuclear phagocytes and granulo-

cytes at various stages of phagocytosis of pyogenic cocci, which contributes to more severe clinical course, and frequent relapse of this diseases [2]. It was also proved that the colon microbiota plays an important role in the formation of homeostasis and immune response. A relationship between the condition of the colon microbiota, indices of systemic immunity and phagocytosis and nature of clinical manifestations of acne justifying differentiated administration of probiotics and immunomodulation therapy in the comprehensive therapy were found [5].

According to modern standards [6,7,8,9], the treatment of acne is carried out in various ways: patients with mild acne are prescribed an external antibacterial and anti-inflammatory therapy (topical antibiotics, topical retinoid medicines, azelaic acid, benzoyl peroxide) only, but in case of moderate and severe forms, comprehensive treatment

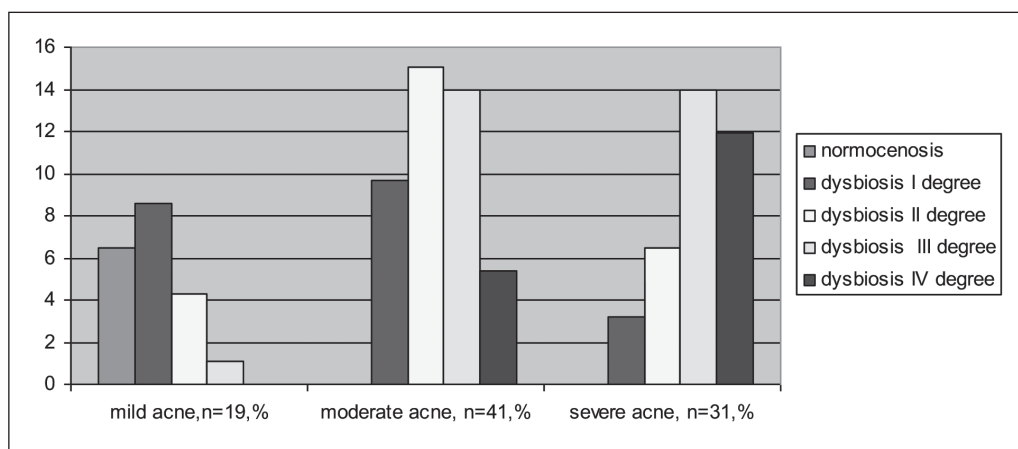


Figure 1. Distribution of patients with different severity of acne according to the degree of dysbiosis.

including systemic antibacterial, immunotropic, anti-inflammatory drugs, oral retinoid, low-dose birth control pills and other therapies are applied [6].

THE AIM

The objective of the study is to determine the evolution of phagocytosis indices in patients with acne under different comprehensive treatments, using oral antibiotics, immunotherapy (autohemotherapy), probiotics and low-dose birth control pills.

MATERIALS AND METHODS

We observed 93 women with acne aged from 18 to 25 years old. In 19 (20,43 %) patients mild acne was diagnosed, in 41 (44,09%) – moderate acne, in 33 (35,48 %) persons – severe acne, 54 (58,06%) persons suffered from acne up to 1 year, 39 (41,93%) – from 1 to 3 years. The control group consisted of 35 healthy individuals (donors) of the similar age. Patients were being observed during a year.

The considered criteria for the study were the following: patient's age - 18 years old or more; clinical manifestations of acne, absence of chronic physical illness or exacerbation at the time of the examination.

To assess the state of phagocytosis in patients with acne vulgaris, we determined phagocytic activity (PA) and phagocytic index (PI) of polymorphonuclear leukocytes, nitro blue tetrazolium recovery test (NBT test spontaneous) and NBT-test pyrogenal stimulated by the recognized methods.

Statistical analysis of the results of research was carried out by the methods of statistical analysis using software (Excel, Statistica 6.0), the difference of averages was considered probable at $p < 0.05$.

RESULTS AND DISCUSSION

Before treatment, patients with acne had probable decrease in PI (by 31.7%, $p < 0.001$) with the downward trend of PA (by 8.82%, $p > 0.05$), characterizing the initial stages of phagocytic process, as well as probable reduction of spontaneous NBT-test (by 24.8%, $p < 0.01$) and stimulated NBT

test (by 22.2%, $p < 0.001$), which represent the final stage of the process of phagocytosis. At the same time, women with acne had concomitant dysbiosis of the large intestine cavity of I- IV degree and interdependence between changes of parameters of systemic immunity and phagocytosis, the degree of intestinal dysbiosis and severity of clinical course of acne was established (Figure 1), justifying the administration of probiotics and immunotropic therapy for these patients.

In order to optimize the treatment of acne, taking into consideration the found changes in systemic immunity indices of these patients, phagocytosis and colon microbiota, we developed a complex therapeutic method which suggests the administration of immunotherapy (autohemotherapy) [10,11], probiotic containing *Escherichia coli* Nissle 1917, low-dose birth control pills that have antiandrogenic effect and oral antibiotics (including *doxycycline*).

To determine the effectiveness of the developed method of combined therapy of acne, the patients under study were divided into 3 groups, using random method, and women in the groups were of similar age and clinical forms of acne. The first comparative group included 29 women who received systemic therapy, including oral antibiotics (including *doxycycline*) 0.1g twice a day during 14 days, probiotic containing *Escherichia coli* Nissle 1917 (1 capsule once a day during 1 month two times a year) and autohemotherapy according to the admitted scheme (2.0-4.0-6.0-8.0-10.0-8.0-6.0-4.0-2.0); the second comparative group consisted of 33 patients who were administered probiotic containing *Escherichia coli* Nissle 1917, low-dose birth control pills (for 12 month) and autohemotherapy; and the third (basic) group numbered 31 patients who were administered a comprehensive systemic therapy treatment which included oral antibiotics (including *doxycycline*) 0.1g twice a day 14 days, probiotic containing *Escherichia coli* Nissle 1917 (1 capsule once a day during 1 month two times a year), low-dose birth control pills (during 12 months) and autohemotherapy. All patients also received external antibacterial and anti-inflammatory therapy: the women with mild acne – azelaic acid, benzoyl peroxide, with moderate and severe acne – additionally topical retinoid medicines.

The evaluation of the results of different treatments for acne was conducted basically on the analysis of the evolution of clinical and laboratory indices of blood including those of phagocytosis, that are shown in the table.

Table I. Evolution of phagocytosis indices in patients with pyoderma after different therapies(M±m)

Indices, measurement units	Patients with acne (n=93)			Control group (n=35)	
	1 st group (n ₁ =29)	2 nd group (n ₂ =33)	3 rd group (n ₃ =31)		
Phagocytic activity, %	Before treatment	54.9±1.65	54.1±2.08 p ₁₋₂ >0.05	55.9±2.54 p ₁₋₃ >0.05; p ₂₋₃ >0.05	62.9±4.28
	After treatment	58.5±1.34	57.9±1.64 p ₁₋₂ >0.05	62.6±1.92 p ₁₋₃ >0.05; p ₂₋₃ >0.05	
	P (before/after treatment)	P>0.05	P>0.05	P<0.05	
Phagocytic index	Before treatment	4.01±0.406**	4.08±0.264*** p ₁₋₂ >0.05	4.26±0.298*** p ₁₋₃ >0.05; p ₂₋₃ >0.05	6.88±0.540
	After treatment	5.06±0.302**	5.56±0.242* p ₁₋₂ >0.05	6.12±0.242 p ₁₋₃ <0.01; p ₂₋₃ >0.05	
	P (before/after treatment)	P<0.05	P<0.001	P<0.001	
spontaneous NBT-test	Before treatment	9.88±0.224**	10.1±0.598* p ₁₋₂ >0.05	10.0±0.709* p ₁₋₃ >0.05; p ₂₋₃ >0.05	12.5±0.850
	After treatment	11.4±0.244	11.9±0.672 p ₁₋₂ >0.05	12.6±0.624 p ₁₋₃ >0.05; p ₂₋₃ >0.05	
	P (before/after treatment)	P<0.01	P<0.05	P<0.01	
stimulated NBT test	Before treatment	21.4±0.972***	21.8±0.859*** p ₁₋₂ >0.05	20.8±0.698*** p ₁₋₃ >0.05; p ₂₋₃ >0.05	29.3±0.723
	After treatment	24.2±0.634***	24.9±0.436*** p ₁₋₂ >0.05	27.2±0.648* p ₁₋₃ <0.01; p ₂₋₃ <0.01	
	P (before/after treatment)	P<0.05	P<0.01	P<0.001	

Notes:

- * – The degree of probability of the indices deference relative to control group of patients:
* – p<0.05; ** – p<0.01; *** – p<0.001.
- p1-2, p1-3, p2-4 – probability of the indices deference in patients of different groups.
- P – probability of the indices deference in the groups of patients before and after the treatment.

According to the results of the conducted studies (Table 1), patients of the 1st comparative group, who received systemic therapy, including oral antibiotics, probiotic and autohemotherapy, were likely to increase their PI by 26.18% (p <0.05), NBT-test of spontaneous and stimulated (by 15.38%, p<0.01 and 13.08% respectively, p <0.05), but preserving significant difference of PA and stimulated NBT-test with those of the control group (a decrease by 26.45%, p <0.001 and 17.41%, p <0.001 respectively).

Women with acne in the second comparative group, due to the use of probiotic, low-dose birth control pills, autohemotherapy at the end of treatment, showed probable growth of PI rates by 36.27% (p <0.001), NBT-test of spontaneous and stimulated (by 17.82%, p <0.05 and 14.22%, p <0.01 respectively), but without probable difference to the patients of the first comparative group with preserving significant difference of PI and stimulated NBT-test with the same parameters in control group (a decrease by 19.19%, p <0.05 and 15.02%, p <0.001 respectively).

However, patients with acne in the core group who received combined therapy which included oral antibiotic, probiotic, low-dose birth control pills (for 12 month) and

autohemotherapy, experienced probable increase in PI and PA (by 43.66%, p <0.001 and 11.98%, p <0.05 respectively), spontaneous NBT-test (by 20.6%, p <0.01) as well as stimulated NBT test (by 30.77%, p <0.001) with the approximation of most of them, except NBT-test stimulated, to the values of those in the control group.

Analysis of the studied parameters of phagocytosis at the end of treatment also showed a significant increase in patients of the core group compared to those of patients in other comparative groups. Thus, the rate of PI at the end of end of the treatment in patients of the main group was significantly higher both comparing to the indices of the patients in the 1st comparison group (by 20.95%, p <0.01), while stimulated NBT test relative to the 1st comparative group (by 12.39%, p <0.01) and to the 2st comparative group (by 9.24%, p <0.01). The obtained better results on the evolution of the phagocytosis indices in patients of the main group could be related to the following: direct stimulating effect of immunotherapy, low-dose birth control pills have regulatory influence on the homeostasis of woman's organism and by a decrease of microbial intestinal load on macrophages and granulocytes as a result of normalizing probiotic action on concomitant dysbiotic disturbances of the large intestine in such patients.

CONCLUSIONS

Using combined therapy with the inclusion of oral antibiotic, probiotic, low-dose birth control pills and autohemotherapy for women with acne occurring against the backdrop of a sluggish process of phagocytosis and concomitant intestinal dysbiosis leads to normalization of the leading indices of phagocytosis (PI, PA, NBT tests both spontaneous and stimulated), and enhances their phagocytic activity both during capture and formation of bactericidal activity and in the final stages of phagocytosis, justifying the feasibility of a combined use of antibiotics, probiotic, low-dose birth control pills and autohemotherapy in the treatment of acne.

In the future we are planning to determine and analyze the evolution of other homeostasis indices in a combined treatment of patients, suffering from acne by using oral antibiotics, probiotic, low-dose birth control pills and autohemotherapy as a complex.

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Received: 14.09.2017

Accepted: 22.12.2017

РОЛЬ ГЕНОВ РЕНИН-АНГИОТЕНЗИНОВОЙ СИСТЕМЫ В РАЗВИТИИ НЕБЛАГОПРИЯТНЫХ ИСХОДОВ ЛЕЧЕНИЯ ТЯЖЕЛЫХ ВНУТРИЖЕЛУДОЧКОВЫХ КРОВОИЗЛИЯНИЙ У ПРЕЖДЕВРЕМЕННО РОЖДЕННЫХ ДЕТЕЙ

THE ROLE OF GENES OF RENIN-ANGIOTENSIN SYSTEM IN THE DEVELOPMENT OF ADVERSE OUTCOMES OF TREATMENT IN SEVERE INTRAVENTRICULAR HEMORRHAGES IN PREMATURE INFANTS

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РЕЗЮМЕ

Введение: Внутрижелудочковые кровоизлияния (ВЖК) являются причиной повышенной заболеваемости и смертности преждевременно рожденных детей и ассоциируются с неблагоприятными неврологическими исходами.

Цель: Подтвердить роль генов ренин-ангиотензиновой системы в развитии неблагоприятных исходов лечения тяжелых ВЖК у преждевременно рожденных детей.

Материалы и методы: Проведено проспективное исследование, в которое включено 58 новорожденных (средний вес при рождении $1016,8 \pm 52,59$ г, гестационный возраст $26,96 \pm 0,33$ нед.), которые лечились в лечебных учреждениях Полтавской области в течение 2012–2015 гг. Изучали I/D полиморфизм ACE гена, A/C полиморфизм AGT2R1 гена и 4a/b полиморфизм eNOS гена. Распределение генотипа сравнивали между группами с помощью анализа χ^2 .

Результаты исследования: Из 58 детей, включенных в исследование у 33 (56,9%) младенцев развилась вентрикулодилатация, которая у 8 (13,8%) новорожденных прогрессировала в гидроцефалию. 34 (58,6%) младенцев с тяжелыми ВЖК умерли. Средний показатель (медиана) времени смерти детей составил 10,6 суток. Среди детей, которые умерли, достоверно чаще, чем у детей, которые выжили, выявляли сочетание генотипов ID&DD гена ACE+4ab & 4AA гена eNOS и на границе статистической значимости – изолированно генотип 4ab & 4AA гена eNOS. Сочетание генотипа ID+DD ACE гена и AC+CC генотипа AGTR1 гена достоверно чаще оказывалось среди детей с вентрикулодилатацией, чем у детей без нее. Вес при рождении имеет негативные корреляционные тренды с летальными исходами и не имеет – с вентрикулодилатацией и гидроцефалией.

Выводы: Летальные исходы у детей с ВЖК ассоциируются с весом при рождении, а также наличием у них сочетания генотипов ID+DD гена ACE и 4ab+4aa гена eNOS.

КЛЮЧЕВЫЕ СЛОВА: тяжелые внутрижелудочковые кровоизлияния, ренин-ангиотензиновая система, преждевременно рожденный ребенок, вентрикулодилатация, постгеморрагическая гидроцефалия.

ABSTRACT

Introduction: Intraventricular hemorrhage (IVH) causes increased morbidity and mortality in premature infants and is associated with adverse neurological outcomes.

The aim of the research is to confirm the role of genes of renin-angiotensin system in the development of adverse outcomes of treatment of severe IVC in preterm.

Materials and methods: A prospective study was conducted, which included 58 premature infants (average birth weight 1016.8 ± 52.59 g, gestational age 26.96 ± 0.33 weeks), who were treated at medical institutions in Poltava region during 2012–2015. I/D polymorphism of ACE gene, A/C polymorphism of AGT2R1 gene and 4a/b polymorphism of the eNOS gene were studied. The distribution of the genotype was compared between groups using the χ^2 analysis.

Results: Out of 58 children enrolled in the study, 33 (56.9%) of infants developed ventricular dilatation, which in 8 (13.8%) of the newborns progressed to hydrocephalus. Thirty-four (58.6%) infants with severe IVHs died. The average (median) time of death of infants was 10.6 days. Among children who died, a combination of genotypes ID & DD of the gene ACE +4ab & 4AA of the eNOS gene was found significantly more often than in children who survived, and at the border of statistical significance – the isolated genotype 4ab & 4aa of the eNOS gene. The combination of genotype ID+DD of the ACE gene and the AC + CC genotype of the AGTR1 gene was significantly more frequent among children with ventricular dilatation than in children without it. The weight at birth have negative correlation trends with lethal outcomes and do not have with ventricular dilatation and hydrocephalus.

Conclusions: Lethal outcomes in children with IVH are associated with weight at birth, as well as the presence of a combination of genotypes ID+DD of the ACE gene and 4ab+4aa of the eNOS gene.

KEY WORDS: severe intraventricular hemorrhage, renin-angiotensin system, preterm, posthemorrhagic hydrocephalus, ventricular dilatation

ВВЕДЕНИЕ

Внутрижелудочковые кровоизлияния (ВЖК) являются причиной повышенной заболеваемости и смертности преждевременно рожденных детей и ассоциируются с неблагоприятными неврологическими исходами [1,2]. Несмотря на снижение частоты ВЖК всех степеней, частота тяжелых ВЖК (III-IV степени) остается на прежнем уровне, поскольку постоянно увеличивается выживаемость детей с очень низким весом при рождении [3,4]. Согласно данным многоцентровых исследований в когорте младенцев с очень малым весом при рождении, частота ВЖК варьирует от 15% до 42%, а тяжелых ВЖК – от 7% до 16% случаев [5,6]. Недавние исследования показывают, что уровень смертности у новорожденных с ВЖК III степени, родившихся до 28 недель гестации, составляет около 30%, а у детей с ВЖК IV степени – около 60%. В Полтавской области, начиная с 2010 года, показатели летальности среди преждевременно рожденных детей при наличии ВШК, как и в целом в Украине, не снижаются и составляют 20-21% [7].

У около 35% младенцев с тяжелым ВЖК развивается постгеморрагическая гидроцефалия (ПГГ) [5]. К настоящему времени только в некоторых исследованиях были рассмотрены факторы риска развития неблагоприятных исходов у преждевременно рожденных детей с ВЖК [9, 10], однако не изучен вклад генетической детерминанты в их возникновение.

В предыдущих исследованиях было сообщено о возможной связи между полиморфизмом ангиотензин-превращающего фермента (ACE), рецептора 1 типа ангиотензина (AGTR1) и риском развития бронхо-легочной дисплазии [11,12], ретинопатии [13], синдрома артериальной гипотензии [14] и асфиксии новорожденного [15]. Ренин-ангиотензиновая система (РАС) и эндотелиальная NO-синтаза (eNOS) принимает важное участие в регулировании системного артериального давления и объема циркулирующей крови, а ее генетические модификации могут повлиять на последствия заболеваний неонатального периода у недоношенных младенцев. Литературные источники свидетельствуют о благотворном влиянии окиси азота (NO) на рост и защиту сосудов у недоношенных детей [16], что подтверждается данными о наличии связи между активностью генов, кодирующих синтез eNOS и риском развития ВЖК в этой популяции [17]. Таким образом, сосудистые действия eNOS могут быть критическими в предотвращении кровоизлияний в развивающийся головной мозг.

Ангиотензин-конвертирующий фермент (ACE) – мембранный белок, который имеет важное значение в регуляции артериального давления, сосудистого тонуса микроциркуляторного русла. Однако, полиморфизм ACE гена не влияет на нарушения структуры энзима или его функциональную способность, а лишь

коррелирует с его концентрацией в организме [18]. Проведенные научные исследования доказали кодоминантный тип наследования аллелей и обнаружили нейротекторное влияние I-варианта полиморфного гена при ишемическом поражении нервной системы, зависимость от наличия D-варианта гена и повышенные риски инициации провоспалительной активности нейтрофилов [18–20].

На основании этих данных мы выдвинули гипотезу, что на возникновение неблагоприятных исходов лечения тяжелых ВЖК у недоношенных детей может влиять полиморфизм генов, кодирующих фермент eNOS и белки ренин-ангиотензиновой системы (AGTR1, ACE).

ЦЕЛЬ ИССЛЕДОВАНИЯ

Подтвердить роль генов ренин-ангиотензиновой системы в развитии неблагоприятных исходов лечения тяжелых ВЖК у недоношенных детей.

МАТЕРИАЛЫ И МЕТОДЫ

Проведено проспективное исследование, в которое включено 58 недоношенных детей (мальчиков – 30 [51,72%], девочек – 28 [48,28%]), находящихся на лечении в акушерских и детских лечебных учреждениях Полтавской области в течение 2012–2015 гг. Критериями отбора детей в группы исследования стали: наличие ВЖК III–IV степени, которую выставляли по классификации Papile [21], гестационный возраст менее 32 недель, масса тела при рождении менее 1500 г. Факторами исключения стали: наличие врожденных аномалий развития, масса новорожденного более 1500 г, подтвержденная TORCH-инфекция, дети, рожденные от многоплодной беременности, с летальным исходом одного из детей. Среди младенцев с ВЖК исследовали частоту таких неблагоприятных исходов: летальные случаи, вентрикулодилатацию и гидроцефалию. В дальнейшем, для доказательства роли полиморфных вариантов генов РАС в развитии указанных состояний, дети с ВШК тяжелой степени в зависимости от наличия или отсутствия исследуемого исхода распределялись на 2 группы. Клинические и демографические данные детей, включенных в исследование, представлены в табл. I. Дизайн, методики клинических и генетических исследований получили одобрение биоэтической комиссией ВГУЗУ «Украинская медицинская стоматологическая академия», Полтава, Украина.

Нами изучен I/D полиморфизм ACE гена, A/C полиморфизм AGT2R1 гена и 4a/b полиморфизм eNOS гена. Материалом для проведения лабораторных исследований служила кровь (0,25 мл) новорожденных, которую брали на 1–3 сутки жизни. Для определения полиморфных вариантов генов ACE, AGT2R1 и eNOS проводили полимеразную цепную реакцию с последующим рестрикционным анализом продуктов реакции амплификации. Детекцию проводили в агарозном геле, амплификацию выделенной

Таблица I. Демографические и клинические характеристики новорожденных, включенных в исследование, М±m; n (%)

Показатели	n=58
Вес при рождении (г)	1016,8±52,59
Гестационный возраст (нед.)	26,96±0,33
Кесарево сечение	29 (50,0)
Аntenатальное использование стероидов	23 (39,6)
Оценка по Апгар на 5 минуте (баллы)	5,7±0,16
Использование сурфактант-заместительных препаратов	33(56,9)
Искусственная вентиляция легких	43 (74,1)
Респираторный дистресс синдром III-IV ст.	34 (58,6)
Сепсис	25 (43,1)
Некротизирующий энтероколит	5 (8,6)
Вентрикулодилатация	33 (56,9)
Гидроцефалия	8 (13,8)

Таблица II. Распределение полиморфных вариантов генов eNOS и ренин-ангиотензиновой системы в группе детей, которые выжили, и в группе детей, которые умерли, n (%)

Ген	Генотип	Дети с ВЖК III-IV ст., выжившие, n=24	Дети с ВЖК III-IV ст., умершие, n=34	p
ACE	II	4 (16,67)	9 (26,47)	0,378
	ID&DD	20 (83,33)	25 (73,53)	
AGTR1	AA	15 (62,5)	14 (41,18)	0,110
	AC&CC	9 (37,5)	20 (58,82)	
eNOS	bb	19 (79,17)	19 (55,88)	0,058
	4ab&4aa	5 (20,83)	15 (44,12)	
ACE+ AGTR1	II+AA	16 (66,67)	20 (58,82)	0,584
	ID&DD+AC&CC	8 (33,33)	14 (41,18)	
ACE+ eNOS	II+bb	21 (87,5)	21 (61,76)	0,031
	ID&DD+4ab&4aa	3 (12,5)	13 (38,24)	
AGTR1+eNOS	AA+bb	22 (91,67)	25 (73,53)	0,083
	AC&CC+4ab&4aa	2 (8,33)	9 (26,47)	

Таблица III. Ассоциации между летальными случаями и генотипом 4ab & 4aa изолировано и в сочетании с генотипом ID&DD

Показатели	Простой регрессионный анализ		Множественный регрессионный анализ		
	ОШ (95% ДИ)	p	ОШ (95% ДИ)	p	
I модель	Масса тела при рождении	0,99 (0,995-0,999)	0,003	0,99 (0,995-0,999)	0,010
	4ab & 4aa	2,99 (0,91-9,91)	0,07	3,66 (0,92-14,6)	0,06
II модель	Масса тела при рождении	0,99 (0,995-0,999)	0,003	0,99 (0,995-0,999)	0,008
	ID&DD+4ab&4aa	4,33 (1,07-17,45)	0,04	4,5 (0,96-21,19)	0,05

ДНК – в реакционной смеси с M. Arand. Продукты амплификации участков генов подлежали гидролитическому расщеплению с помощью эндонуклеазы рестрикции Alw261. Амплифицированные фрагменты распределяли с использованием горизонтального электрофореза в 1,5% агарозном геле с окраской бромистым этидием.

Распределение генотипа между группами детей сравнивали с помощью анализа χ^2 . Для изучения

связи между развитием неблагоприятных исходов и весом ребенка при рождении, а также генотипами генов PАС использовали простой логистический регрессионный анализ. Для каждого из потенциальных факторов риска определены отношение шансов и 95% доверительный интервал (ОШ; 95% ДИ). Вычисления статистических величин проводилось с помощью лицензионного пакета программы STATA 11.

Таблица IV. Распределение полиморфных вариантов гена eNOS и ренин-ангиотензиновой системы в группе детей с вентрикулодилатацией и в группе детей без вентрикулодилатации, n (%)

Ген	Генотип	Дети без вентрикулодилатации, n= 25	Дети с вентрикулодилатацией, n= 33	p
ACE	II	5 (20,0)	8 (24,24)	0,477
	ID&DD	20 (80,0)	25 (75,76)	
AGTR1	AA	15 (60,0)	14 (42,42)	0,144
	AC&CC	10 (40,0)	19 (57,58)	
eNOS	bb	16 (64,0)	22 (66,67)	0,525
	4ab&4aa	9 (36,0)	11 (33,33)	
ACE+ AGTR1	II+AA	19 (76,0)	17 (51,52)	0,050
	ID&DD+AC&CC	6 (24,0)	16 (48,48)	
ACE+eNOS	II+ bb	17 (68,0)	25 (75,76)	0,359
	ID&DD+4ab&4aa	8 (32,0)	8 (24,24)	
AGTR1+eNOS	AA+bb	22 (80,0)	25 (75,76)	0,202
	AC&CC+4ab&4aa	3 (12,0)	8 (24,24)	

Таблица V. Распределение полиморфных вариантов гена eNOS и ренин-ангиотензиновой системы в группе детей с гидроцефалией и в группе детей без гидроцефалии, n (%)

Ген	Генотип	Дети без гидроцефалии, n=50	Дети с гидроцефалией, n=8	p
ACE	II	10 (20,0)	(37,5)	0,248
	ID&DD	40 (80,0)	5 (62,5)	
AGTR1	AA	25 (50,0)	4 (50,0)	0,647
	AC&CC	25 (50,0)	4 (50,0)	
eNOS	bb	32 (64,0)	6 (75,0)	0,431
	4ab&4aa	18 (36,0)	2 (25,0)	
ACE+AGTR1	II+AA	31 (62,0)	5 (62,5)	0,649
	ID&DD+AC&CC	19 (38,0)	3 (37,5)	
ACE+eNOS	II+bb	32 (70,0)	7 (87,5)	0,287
	ID&DD+4ab&4aa	15 (30,0)	1 (12,5)	
AGTR1+eNOS	4aa+4bb	40 (80,0)	7 (87,5)	

РЕЗУЛЬТАТЫ ИССЛЕДОВАНИЯ

Из 58 детей, включенных в исследование у 33 (56,9%) младенцев развилась вентрикулодилатация, которая у 8 (13,8%) детей прогрессировала с последующим развитием гидроцефалии. Тридцать четыре (58,6%) новорожденных с тяжелыми ВЖК умерли. Средний показатель (медиана) времени смерти детей составил 10,6 суток (1 квартиль–3,2 суток, третья квартиль–9 суток, min–0,5 суток, max–44,6 суток).

Изучение распределения полиморфных генотипов генов eNOS и ренин-ангиотензиновой системы у обследованных новорожденных с тяжелыми ВЖК показало отсутствие достоверных различий между детьми, которые выжили, и детьми, которые умерли, в частоте определения генетической модели ID+DD гена ACE и генетической модели AC+CC гена AGTR1 (табл. II). Разница между частотой генетической модели 4ab+4aa гена eNOS среди детей двух групп оказалась на грани статистической значимости. Так, доминантная модель

4ab+4aa гена eNOS чаще определялась у детей, которые умерли, чем у выживших детей. Мы предполагаем, что связь на грани статистической значимости между генетической моделью 4ab+4aa eNOS гена и летальными исходами у пациентов с ВЖК при простом логистическом регрессионном анализе объясняется многофакторностью заболевания и наличием у обследованных детей сопутствующей патологии (сепсиса, НЭК, РДС), которая ассоциируется преимущественно с малым гестационным возрастом [1]. Что касается изучения сочетания указанных генотипов у обследуемых детей, то среди детей, которые умерли, достоверно чаще, чем у выживших детей, определялось сочетание D-аллели гена ACE и 4a-аллели гена eNOS. Также обнаружены достоверные позитивные корреляционные тренды между летальным исходом и 4ab+4aa генотипом гена eNOS и сочетанием генотипов ID&DD + 4ab&4aa. Также было определено, что возникновение летальных случаев у преждевременно рожденных детей ассоции-

руется с массой тела ребенка при рождении (табл. III).

При анализе распределения изучаемых генотипов у недоношенных детей с тяжелыми ВЖК в зависимости от наличия или отсутствия у них вентрикулодилатации выяснилось, что сочетание генотипа ID+DD ACE-гена и AC+CC генотипа AGTR1-гена достоверно чаще определялось у детей с вентрикулодилатацией (табл. IV). Частота выявления других исследуемых генотипов в группе детей с вентрикулодилатацией и в группе детей без этой патологии была почти одинаковой. Нами не получено достоверной связи между весом ребенка при рождении и развитием вентрикулодилатации (ОШ 1,000; 95% ДИ 0,999-1,000; $p = 0,185$).

В отличие от вышеизложенного этапа исследования, нами не получено достоверных различий в распределении генотипов ACE, AGTR1, eNOS генов, а также их сочетания в группе детей с гидроцефалией и в группе детей без указанного заболевания (табл. V). Следует отметить, что в нашем исследовании масса тела ребенка при рождении не ассоциируется с развитием ВЖК-индуцированной гидроцефалии (ОШ 1,000; 95% ДИ 0,999-1,000; $p = 0,130$).

ОБСУЖДЕНИЕ

Наше исследование показало, что тяжелые ВЖК являются значимой причиной смертности преждевременно рожденных детей в Полтавской области, так как 58,6% младенцев с этой патологией, включенных в исследование, умерли. На высокие показатели смертности детей при тяжелом ВЖК указывают и другие ученые. Недавние исследования сообщают, что уровень смертности составляет примерно 30% среди новорожденных с ВЖК III ст. и 60% среди детей с ВЖК IV ст., родившихся до 28 недель гестации [2,22]. В нашем исследовании средний гестационный возраст новорожденных был несколько ниже – 26,7 недель.

Средний показатель (медиана) времени смерти детей в нашем исследовании составил 10,6 суток, что свидетельствует о том, что у преждевременно рожденных детей тяжелая степень ВЖК является заболеванием, которое значительно ухудшает их состояние в раннем неонатальном периоде. Об аналогичных результатах свидетельствуют и другие авторы [2].

Гидроцефалия является основным исходом ВЖК [23]. В нашем исследовании заболевание, индуцированное тяжелым ВЖК, развилось у 8 (13,8%) младенцев, среди которых 4 (50%) ребенка умерли. То есть, среди детей, включенных в исследование, летальные случаи или гидроцефалия возникли у 38 (65,6%) детей. Об аналогичной частоте развития этих неблагоприятных исходов указывают и другие исследователи. Так, по данным Korean Neonatal Network смерть или гидроцефалия наблюдались соответственно у 52,7% младенцев с ВЖК III ст. и 86,7% младенцев с ВЖК IV ст.

Нами выявлены негативные корреляционные тренды летальных исходов с массой тела при рождении, что соответствует предыдущим отчетам, полученных

Canadian Neonatal Network [24], National Institute of Child Health and Human Development the Neonatal Research Network [4] и European Neonatal Network [25].

Точный механизм прогрессирования ВЖК с последующим развитием гидроцефалии полностью не выяснен. Считается, что индуцированное кровью воспаление в субарахноидальных пространствах способствует образованию микросгустков и дальнейшему развитию облитерирующего арахнодита, который, в свою очередь, снижает резорбцию спинномозговой жидкости [26–29]. Предыдущие исследования показали, что ПГГ индуцирует ишемию, повреждение аксонов олигодендроцитов в белом веществе, что в результате приводит к двигательной или когнитивной дисфункции [10,28]. Современная неонатология располагает только несколькими исследованиями, в которых сообщается о факторах риска развития неблагоприятных исходов при ВЖК [9,10], при этом роль генов PAC в этом процессе практически не исследована.

В данном исследовании мы оценили возможную связь между полиморфизмом генов eNOS, AGTR1, ACE и развитием неблагоприятных исходов лечения тяжелых ВЖК, которые возникают среди преждевременно рожденных младенцев, а именно: летальных случаев, вентрикулодилатации и гидроцефалии. Наши данные показывают, что носители а-аллели 4a4b полиморфизма eNOS гена, а также носители сочетания а-аллели eNOS гена и D-аллели ACE-гена имеют повышенные риски развития летальных исходов. В то же время, младенцы с сочетанием генотипов ID+DD гена ACE и AC+CC гена AGTR1 имеют повышенные риски развития вентрикулодилатации.

Сегодня хорошо известны патофизиологические механизмы NO, которые могут защищать головной мозг недоношенных детей от поражения, а при дефиците этой важной молекулы, наоборот, создавать условия, способствующие повреждению головного мозга [30]. Оксид азота – это многофункциональная молекула, которая участвует в большом количестве биологических реакций, например, регуляции местного артериального давления, способствуя мозговой вазодилатации [31], обеспечивая тем самым адекватное кровообращение тканей и органов; противодействует веществам (эндотелину I, ангиотензину II), которые вызывают сильную вазоконстрикцию; подавляет агрегацию и адгезию тромбоцитов путем уменьшения продукции эндотелием фактора активации тромбоцитов (PAF), защищает стенки сосудов, ингибируя окисления липидов и инактивируя свободные радикалы кислорода [16,32], а также ингибирует пролиферацию сосудистых гладкомышечных клеток.

Учитывая решающую роль NO в содействии ангиогенезу в течение антенатального/неонатального периода [33], можно обоснованно предположить, что носители а-аллели 4ab полиморфизма eNOS гена имеют повышенные риски развития летальных исходов из-за уменьшения синтеза эндотелиального NO, который, в

свою очередь, ухудшает рост и формирование сосудов не только в головном мозге, но и в других органах.

ВЫВОДЫ

Летальные исходы у детей с ВЖК ассоциируются с весом при рождении, а также наличием у них сочетания генотипов ID+DD гена *ACE* и 4ab+4aa гена *eNOS*.

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Робота являється фрагментом науково-дослідницької роботи Государственного учреждения «Институт педиатрии, акушерства и гинекологии Национальной Академии медицинских наук Украины», государственный регистрационный номер: 0117U004538 «Разработать и внедрить систему медико-психологического сопровождения для новорожденных групп риска с формированием хронических заболеваний, инвалидности и задержки развития».

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Прислана: 10.10.2017

Утверждена: 30.01.2018

**MINISTRY OF HEALTH OF UKRAINE
HIGH STATE EDUCATIONAL ESTABLISHMENT OF UKRAINE
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Poltava Days of Public Health

DEAR COLLEAGUES!

In accordance with the approved by the Ministry of Education and Science of Ukraine and the Ukrainian Institute of Scientific and Technical Expertise and Information “The Register of Conferences, Symposiums, Scientific and Practical Conferences and Plenum Meetings to be held in 2018”, we have the honor to invite you to participate in the All-Ukrainian scientific and practical conference with international participation **“Poltava Days of Public Health”**, which will be held on **May 25, 2018**, on the basis of the High State Educational Establishment of Ukraine “Ukrainian Medical Stomatological Academy” (Poltava, Ukraine).

MAIN TOPICS OF THE CONFERENCE:

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TYPES OF PARTICIPATION IN THE CONFERENCE

- oral report
- poster presentation
- publication of articles
- publication of abstracts
- participant (listener)

WORKING LANGUAGES OF THE CONFERENCE: Ukrainian, Russian, English.

Registration form and all materials for participation in the Conference should have been sent by April, **27, 2018**.

All necessary information regarding participation is available at the conference organizing committee.

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Thanks in advance for your participation in the Conference!

THE STUDY OF LEUKOCYTE PHAGOCYtic ACTIVITY IN THE PRESENCE OF HERPETIC INFECTION AND STROKE

BADANIE AKTYWNOŚCI FAGOCYTARNEJ LEUKOCYtÓW PRZY WSPÓŁISTNIENIU ZAKAŻENIA OPRYSZCZKĄ I UDARU

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ABSTRACT

Introduction: Post-stroke complications are one of the urgent and insufficiently resolved problems. According to different literature data 23% to 65% of patients suffer from the post-stroke development of an infectious process. Herpes simplex virus type 1 and 2 can also be etiological factors of stroke development, however their reactivation is seldom mentioned in clinical observations. The development of immune suppression is considered to be the cause of these complications.

The aim: The current study aims at determining post-stroke changes in leukocyte component of the immunity and in the presence of concomitant herpetic infection as well as at finding changes in phagocytosis parameters during antiviral treatment.

Materials and methods: The experiments were carried out on mice of the Balb/c line. The animals were infected with the herpes simplex virus type I, and 30 days later hemorrhagic stroke was simulated by administering 0.1 ml of autoblood into the right hemisphere. Following the acute stroke some animals were given acyclovir, proteflazid or altabor. From the animals' blood leukocytes were obtained and phagocytic activity and production of reactive oxygen species of granulocytes and agranulocytes in relation to fluorescent *E.coli* bacteria were studied by flow cytometry.

Results: The experiment revealed significant changes in the redistribution between two major types of leukocytes in mice with stroke (an increased number of agranulocytes by 19.9%) and decreased phagocytosis activity, in the animals infected with herpes simplex virus type I in particular. Ischemic brain damage had an immunosuppressive effect on blood leukocytes. For comparison a significant increase in phagocyte count in leukocytes was found in the case of viral infection. The use of drugs with antiviral effects did not affect the activity of granulocytes / agranulocytes.

Conclusion: Stroke can be the cause of latent herpes virus infection reactivation and has essential negative effect on immune characteristics of leukocytes that remain unchanged with the use of antiviral agents.

KEY WORDS: stroke, herpes simplex virus type I, leucocytes, acyclovir, proteflazid, altabor.

Wiad Lek 2018, 71, 1 cz. II, 155-159

INTRODUCTION

Stroke is one of the main causes of disability and death around the world [1]. With the increased incidence of stroke the growing number of its concurrent complications is being registered. One of the most prevalent complications of the stroke is infection. Clinical and experimental studies show that stroke impairs interaction between the central nervous system and the immune system, leading to the development of bacterial and viral infections [2,3,4,5].

According to different literature data 23% to 65% of patients suffer from the post-stroke development of an infectious process, with pneumonia and urinary tract infections being the most common [6]. The most frequently found bacterial agents include pathogens from *Streptococcus*, *Klebsiella*, and *Staphylococcus* genii

[7]. Although the authors believe that a large proportion of infectious diseases has viral etiology, they are not always diagnosed and managed appropriately [8]. Herpetic infections belong to viral agents that are often mentioned in clinical research. Herpes simplex virus type 1 and 2 can also be etiological factors of stroke development, however their reactivation is seldom mentioned in clinical observations [9,10]. The development of immune suppression is considered to be the cause of these complications.

More detailed research of pathophysiological processes occurring after the stroke is needed for determining potential therapeutic targets to improve the treatment outcomes and prevent complications of the disease. Known, for different diseases the first indicator is the study of blood [11].

THE AIM

This study aimed at determining post-stroke changes in leukocyte component of the immunity and in the presence of concomitant herpetic infection as well as at finding changes in phagocytosis parameters during antiviral treatment.

MATERIALS AND METHODS

The experiments were conducted on BALB line mice weighing 18-20 g. The animals were kept under controlled conditions: temperature ($22.0 \pm 2.0^\circ\text{C}$), humidity ($55.0 \pm 5.0\%$) and photoperiod with free access to conventional granulated combined feed and drinking water.

The experimental animals were infected by epidural injection of viral material (freeze-dried HSV type I VC) in the retroorbital area. The development of infectious state symptoms in the control group was registered on day 5-6, followed by reduction of infection manifestations severity and ultimate recovery of the animals. Since that point of time HSV-1 has been transferring into its latent form. This model is convenient for evaluating symptoms manifestation, is characterized by 100% reproducibility and does not require any additional methods of control.

On day 30 after the resolution of viral infection manifestations (weakness, decreased agility, decreased need in food and water) hemorrhagic stroke was simulated in survivors. Simulation of a limited hemorrhage (intracerebral hematoma) in the animals' brain was achieved by administration of 0,1 ml of autoblood to the right hemisphere (L=1,5, H=3,0, AP=1,0) [12].

In all animals the haematoma was located in the right internal capsule (capsula interna dextra) of the brain. It allowed to reproduce the standardized model of intracerebral haematoma that does not require additional verification of the type, volume and localization of the lesion and the corresponding sequelae of the pathological condition were similar in all groups of animals and consistent with the standardization and methodology of the experimental study.

The comparison groups were represented by intact animals, animals with stroke and animals with HSV-I. Antiviral drugs proteflazid (37,2 mg/ml), acyclovir (50 mg/ml) and altabor (5 mg/ml) have been administered intraperitoneally to a part of animals for 10 days after infection and stroke simulation.

The experimental groups were the following:

Group 1 – control intact animals (n=6)

Group 2 – animals with stroke (n=7)

Group 3 – animals with HSV-I (n=7)

Group 4 – animals with HSV-I and stroke (n=7)

Group 5 – animals with HSV-I and stroke+proteflazid (n=6)

Group 6 – animals with HSV-I and stroke+acyclovir (n=6)

Group 7 – animals with HSV-I and stroke+altabor (n=6)

The presence of HSV-I in the infected animals (brain, blood, liver) was proved by dot-ELISA assay and *in vitro* method (in Vero cell culture) (n=3, from all groups).

The animal's blood was drawn in the morning after fasting (for 12 hrs) under light ether anesthesia. To prevent blood clotting heparin was used (50 MO). The leukocytes were obtained from peripheral blood of experimental animals by hemolysis of erythrocytes on the day of experiment. For this purpose 5,0 ml of distilled water were added to 100 μl of peripheral blood followed by addition of 5,0 ml of 1,8% of NaCl solution 20 seconds later. The cells have been spinned down at 400g (R18, 1410 rpm) at 12°C for 5 min and the procedure was repeated one more time. The supernatant was poured off and the volume added up to 10 ml by normal saline. Then the cells have been spinned down for 400 g (R18, 1410 rpm) at 12°C for 5 min. Supernatant was poured off and the cells were resuspended in 500 μl of phosphate-buffered saline (PBS) (pH 7,2).

The production of reactive oxygen species (ROS) by leukocytes was measured using 2',7'-dichlorofluorescein diacetate (2',7'-Dichlorofluorescein diacetate MW 485.27, 35845, Sigma-Aldrich) in final concentration of 25 μM according to the methodology [13]. After incubation (+ 37°C) for 45 min in the place protected from sun rays the cells were washed in 10 ml PBS buffer and spinned down by centrifugation at 400 g (R18, 1410 rpm) at 12°C for 5 min. The pellet was resuspended in 500 μl of PBS. The intensity of the studied samples emission was registered by channel logFL1 (515-535 nm) in flowcytometer COULTER EPICS XL (Beckman Coulter, USA), equipped with argon laser (λ of excitation = 488 nm).

The redistribution among different populations of leukocytes was assessed using two parameters of COULTER EPICS XL flow cytometer (Beckman Coulter, USA), by the value of forward (FS, size of the cells) and side light scattering (SS, granularity of cells).

The percentage of phagocytosing cells and engulfing of live fluorescent bacteria by macrophages in samples was evaluated using live fluorescent bacteria *E. coli* following methodology similar to the described one [14]. The cells have been incubated for 90 min at 37°C with live fluorescent bacteria *E. coli* in concentration of 6×10^6 bacteria per ml. Flowcytometry on COULTER EPICS XL (Beckman Coulter, USA) by channel log FL1 (515-535 nm) was conducted after washing.

The principle of phagocytic activity method is based on engulfing of *E. coli*, expressing green fluorescent protein (Green Fluorescent Protein, GFP) by neutrophils, monocytes and macrophages (by phagocytosis). This protein has mol. weight of 26,9 kDa and fluoresces with green light when excited by blue light (laser, 488 nm). Accordingly, the more bacteria have been engulfed by the cell the higher the fluorescence intensity of GFP.

More than 10000 occurrences from each sample were analyzed. The results were processed using program FCS Express V3.

Statistical processing of the obtained samples was conducted using program Statistica 6.0. The samples were compared using the Student's test. Results were presented as a mean (M) and standard deviation of the mean ($\pm m$). The difference was considered to be statistically significant at $p < 0,05$.

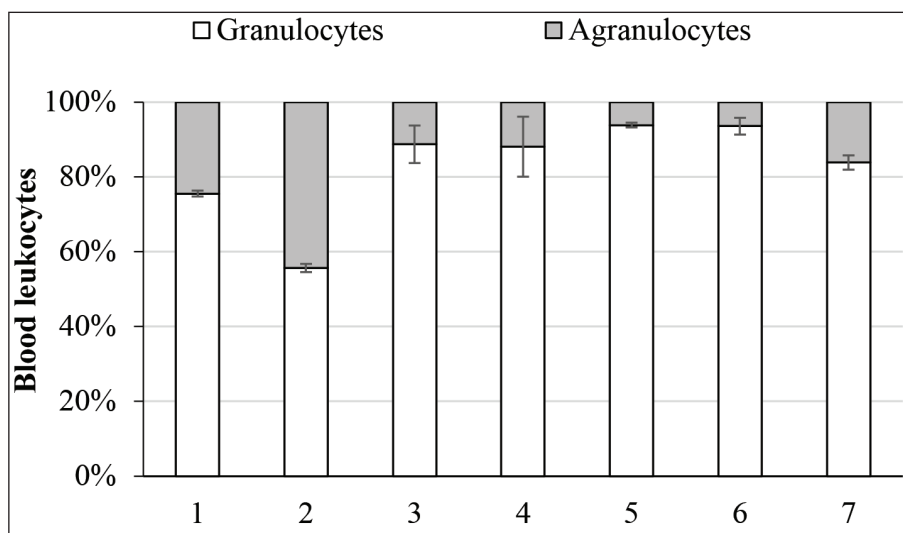


Fig. 1. Redistribution of blood leukocytes in groups of experimental animals (n=5). * - parameters differ from the group 1 (P<0,05) # - parameters differ from the group 2 (P<0,05)

RESULTS AND DISCUSSION

Significant difference in distribution between two main types of leukocytes was found in experimental conditions (Fig. 1). Animals with stroke (group 2) were characterized by a shift in leukocyte ratio to the agranular leukocyte side. Average ratio between leukocytes has shifted by 19,9% to the agranulocyte side ($p<0,05$).

The number of granulocytes increased in groups of animals with HSV-I (group 3) by 13,2% ($p=0,05$) on the average and by 33,1% ($p<0,05$) as compared to group 2.

In groups with HSV and stroke (groups 4-7) the granulocytes/agranulocytes ratio did not differ from data of group 3 and was significantly higher compared to group 2.

The decreased fluorescence intensity of 2',7'-dichlorofluorescein diacetate in granulocytes of animals with stroke (group 2) was found as compared to control, moreover this value did not differ from control or even had tendency to increase in groups infected with HSV-I as it was shown in groups 4-7 (Fig. 2). There was no sufficient difference between comparison groups 4-7. A slight decrease of granulocytes fluorescence intensity (8,6%, $p<0,05$) was shown for group 5 as compared to group 4.

Agranulocytes were characterised by increased fluorescence intensity in all groups with HSV- I (groups 3-7) as compared to control. Fluorescence intensity of 2',7'-dichlorofluorescein diacetate is considered to be directly proportional to the content of such ROS as hydroxyl radical OH^\cdot and peroxynitrite (ONOO^\cdot) in cells. Thus, the mentioned increase of the studied value is a manifestation of intensification of ROS production in leukocytes in the presence of HSV-I.

The fluorescence rate in leucocytes from groups 4-7 did not statistically differ from that in group 3. It indicates the effect of HSV- I on functional state of leucocytes and their production of ROS.

While evaluating phagocytic index (ratio of phagocytosing cells to the total amount of cells in the studied leukocyte samples) we have observed its decrease in groups of animals with the simulated stroke. In HSV-I group the phagocytic index did not differ from the control level.

These data show that ischemic damage of brain causes immune-suppressive effect on leukocytes.

Analysis of phagocytic number change, i.e. the number of phagocytosed units of *E.coli* by a single leukocyte also confirms the phenomenon of immune suppression in the stroke group (the decreased fluorescence intensity by 39,1%, $p<0,05$). Moreover, a notable increase of phagocytic index was shown for the group of animals with HSV-I (group 3). These parameters in group 4 did not significantly differ statistically from groups 1 and 3, this is the case with groups 5 and 7 that were administered proteflazid and altabor where that index had also increased.

Thus, the stroke causes immune suppression which is manifested by the decrease of granular leukocytes count and their phagocytic activity. Immune activity of leukocytes in the presence of HSV-I includes the increase of granular leukocyte count and production of ROS by agranulocytes. Stroke with underlying HSV-I has shifted leukocytes ratio to granulocyte side, which were characterized by the dramatic drop of phagocytosis while the decreased number of agranular leukocytes did not differ from the control by the phagocytic number. In the groups, which have received the medicine the leukocyte parameters did not differ from the comparison group and the phagocytic number in groups 6 and 7 was even lower.

Our experimental study has demonstrated the connection between stroke, herpes virus infection and immune disorders. Herpes virus infection is the most common among viral infections and is often latent. Clinical research has shown the connection between blood vessels damage and the development of stroke in the presence of latent or acute form of herpes virus infection [15,16].

In this study an attempt to find a causal relation between stroke and infection reactivation was made. For that purpose stroke was simulated in the animals infected with strain of the virus from the museum (which was deliberately adapted to the research on laboratory mice) followed by the assessment of the functional parameters of leukocytes to identify manifestations of immune suppression. As shown by the study results, the stroke is accompanied

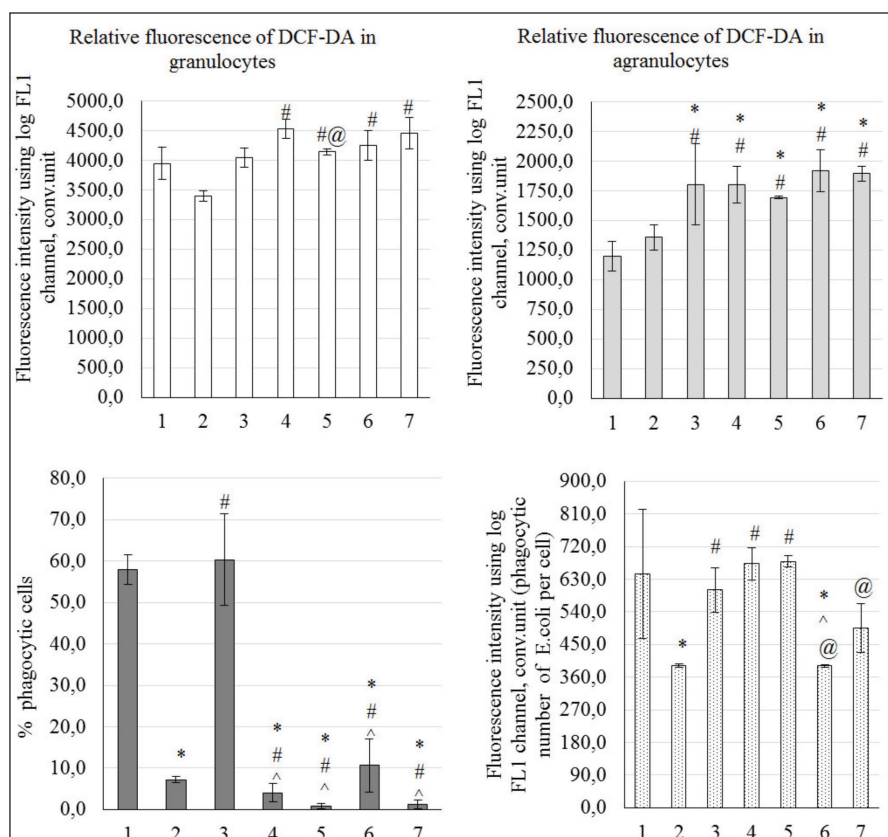


Fig. 2. Functional features of granulocytes and agranulocytes in mice blood
 * - parameters differ from the group 1 (P<0,05)
 # - parameters differ from the group 2 (P<0,05)
 ^ - parameters differ from group 3 (P<0,05)
 @ - parameters differ from the group 4 (P<0,05)

by a significant reduction of the total granulocyte count, their ROS-producing function and phagocytic activity. Similar changes were found in infected animals with stroke. These findings give evidence of the development of post-stroke immune suppression. Moreover there was no significant difference found between groups of animals, which were given antiviral agents and comparison group which had not received any agents. These findings provide additional evidence of the significant negative effect of the stroke on the immune system whereas the impact on the infectious process does not contribute to the recovery of the functional activity of leukocytes.

Unfortunately, the mechanism of post-stroke immune suppression remains unclear. Studies of these disorders in the setting of stroke are focused on two main areas: local immune responses and systemic infections [17]. Different immune cells play different roles in stroke development. Macrophages and monocytes are known to cross the blood-brain barrier and release inflammatory mediators thus increasing infiltration by other leukocytes [18]. Monocytes and macrophages are the main phagocytes and antigen-presenting cells that initiate subsequent immune responses by interacting with T-cells [19]. The authors believe that in case of brain ischemia monocytes utilize the damaged nervous cells thus facilitating regenerative processes. However, simultaneous or concurrent infiltration by neutrophils has negative effect on the extent of brain damage and progression of inflammation [20]. Neutrophils quickly respond to the infectious agent realizing their immune

function by generation of superoxide [21]. Impairment of this function of neutrophils was noted in patients with ischemic and hemorrhagic stroke, which explains the decreased resistance to infections [22].

The pro- and anti-inflammatory mechanisms balance can be directed at limiting the degree of inflammation and promotes reconstitution of immune homeostasis. However there are no doubts that inflammatory processes at the site of ischemia lead to adverse outcomes, development of neurological disorders especially in the presence of co-infections.

Results of clinical researches have demonstrated the low level of lymphocytes, functional deactivation of monocytes, T-helpers and NK-cells during first 6 days after the stroke [23,24], with resistant lymphopenia found in patients with inflammation [25]. Furthermore the decrease of pro-inflammatory cytokines level can also be a factor of the emergence of infection [26]. Another proof of systemic immune disorders is the shrinking of immune organs (spleen, thymus) that was demonstrated in experimental research [27]. These disorders are considered to be the result of hypothalamic-pituitary-adrenal system response, release of adrenocorticotropin and ultimate acute increase of adrenocorticoids in blood [28,29]. Similarly the stroke-induced activation of the sympathetic nervous system leads to secretion of catecholamines by adrenal medulla and nerve endings [30]. Immune cells respond to glucocorticoids and catecholamines and extra stimulation causes apoptosis of lymphocytes, which explains the post-stroke immunodeficiency and other pathological conditions [31,32]. Lymphopenia becomes one of the causes of immune suppression.

CONCLUSION

Thus, stroke can be the cause of latent herpes virus infection reactivation, has essential negative effect on immune characteristics of leukocytes that remain unchanged with the use of antiviral agents.

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Received: 14.09.2017**Accepted:** 22.12.2017

ФАКТОРЫ РИСКА ВОЗНИКНОВЕНИЯ НЕБЛАГОПРИЯТНОГО ТЕЧЕНИЯ ЯЗВЕННОЙ БОЛЕЗНИ ЖЕЛУДКА И ДВЕНАДЦАТИПЕРСТНОЙ КИШКИ

RISK FACTORS FOR ADVERSE COURSE OF GASTRIC AND DUODENAL PEPTIC ULCER

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РЕЗЮМЕ

Введение: Высокая заболеваемость, частые рецидивы, значительные экономические потери - все это даёт основания выделить язвенную болезнь, как наиболее актуальную медико-социальную проблему.

Цель: изучить силу влияния основных факторов риска возникновения, неблагоприятного течения язвенной болезни желудка и двенадцатиперстной кишки.

Материалы и методы: Сформированы группы риска с 12 модифицированных (4) и немодифицированных (8) факторов, каждый из которых имеет свои признаки, градации. Осуществлена количественная оценка факторов, их признаков в виде баллов, по результатам которой определено наиболее информативно значимые.

Результаты: Среди немодифицированных факторов выделено: пол, возраст, отягощённая наследственность, группа крови O(I) Rh+. Доказано наличие риска развития язвенной болезни у мужчин (+2,3 балла) молодого трудоспособного возраста со склонностью передачи по наследственности (+2,3 балла), по мужской линии и у лиц с O(I) Rh+ группой крови (+1,4 балла). Среди модифицированных факторов риска определяющей является инфекция *Helicobacter pylori* (Hp) как предиктор усиления агрессивности (+9,7 балла). Существенным является негативное влияние сопутствующей патологии (+5,0 балла): болезни гепатобиллиарной системы (+3,8 балла), гипертоническая болезнь (+4,0 балла), сахарный диабет (+1,3 балла). Третье место принадлежит нарушению режима питания (+3,7 балла), курению (+3,2 балла) и стрессу (+3,0 балла).

Выводы: По результатам осуществления количественной оценки факторов в виде баллов, наиболее информационно значимыми оказалось наличие инфицирования *H. pylori*, сопутствующей патологии, значение которой возрастает с численностью болезней, а также нерациональный режим питания. Доказана прямая зависимость между наличием ведущих факторов риска развития язвенной болезни, неблагоприятного ее течения и потребностью в медицинской помощи в виде длительности и кратности лечения.

КЛЮЧЕВЫЕ СЛОВА: язвенная болезнь желудка и двенадцатиперстной кишки, факторы риска.

ABSTRACT

Introduction: High morbidity rate, frequent relapses, and significant economic losses give reasons for highlighting the peptic ulcer disease as the most topical medical-statistical problem.

The aim of the study is to assess the influence of the main risk factors on the course of gastric and duodenal peptic ulcer.

Materials and methods: We formed up the risk groups consisted of patients with 12 modified (4) and regular (8) factors, each characterized with its own signs and gradations. We performed the quantitative evaluation of the factors and scored the signs thereof, the results of which were used for determination of the most informative ones.

Results: Among the regular factors, we placed emphasis on gender, age, burdened heredity, and O(I), Rh+ blood type. The risk of peptic ulcer in hereditary tainted young men of the working age with parental lineage (+2.3) and in males with O(I) Rh+ blood type (+1.4) was proved. *Helicobacter pylori* (Hp) infection is a key contributor (a predictor of) to severity of the disease course (+9.7) among the modified risk factors. Negative effect of a concomitant pathology (+5.0), including hepatobiliary lesions (+3.8), hypertension (+4.0), and diabetes mellitus (+1.3) is also significant. Diet violation (+3.7), tobacco smoking (+3.2) and stress (+3.0) were ranked third.

Conclusions: The results of quantitative evaluation of the factors scoring suggest of the underlying *H. pylori* infection (the significance of which is growing along with the growth of the disease incidence) and irrational diet as the most informatively important ones. We have established the direct dependence between the most important peptic ulcer risk factors, severity of the disease, and duration and periodicity of treatment thereof.

KEY WORDS: gastric and duodenal peptic ulcer, risk factors.

ВВЕДЕНИЕ

Болезни органов пищеварения (БОП) занимают третье место за распространенностью, и второе - по количеству обращений всех возрастных групп населения за медицинской помощью после патологии органов дыхания [1]. В частности, обращает на себя внимание тот факт, что даже в первой половине 19-го века язвенная болезнь не носила такого массового характера, как в 20-ом, когда по настоящему наблюдается язвенная эпидемия.

По статистическим данным разных стран, в течение жизни язвенной болезнью страдают от 10 до 20% населения [2]. В последние 80 лет рост заболеваемости язвенной болезни связывают с урбанизацией, миграцией населения, что приводит к несвойственным ранее чрезмерным эмоциональным и физическим перенапряжениям, изменению ритма жизни [3], вредному воздействию шума, загрязнения воздуха и развитию тканевой гипоксии, изменением характера питания, несбалансированным питанием с употреблением большого количества алкогольных напитков [4, 5], неконтролируемым приёмом агрессивных лекарственных средств, наличием сопутствующей патологии, курением [6]. Открытие инфекции *Helicobacter pylori* позволило установить истинную и наиболее частую причину развития язвенной болезни желудка и двенадцатиперстной кишки, вызывающая прогрессирующее повреждение слизистой оболочки желудка [7].

Относительно факторов риска развития БОП авторы отмечают следующие: мужской пол (4:1); генетическая склонность, наличие 0 (I) группы крови, Rh+, HLA-антигены B15, B5, B35; уменьшение активности б1-анти трипсина, б2-макроглобулина; дефицит желудочной слизи (фукогликопротеинов); дефицит секреторного Ig A; расстройства моторики гастро-дуоденальной зоны (повышен тонус n. vagus (ваготония)); курение; психоэмоциональные стрессовые состояния; злоупотребление экстрактными кушаньями (бульоны, копчения), острой, кислой, пряной, грубой, горячей, холодной едой, кофе, алкогольными напитками; нарушение режима питания (длительные перерывы между употреблением еды); употребление медикаментозных средств: нестероидные противовоспалительные препараты (НПВП, глюкокортикостероидов, резерпина). Считается, что регулярное употребление НПВП (прием 3-х и больше доз на неделю в течение одного месяца) может играть решающую роль в возникновении около 4-5 % дуоденальных и до 30 % желудочных язв. Также триггерными факторами являются хронические заболевания: хронические обструктивные заболевания легких, бронхиальная астма, хроническая сердечная недостаточность, цирроз печени, хронический холецистит, панкреатит; вредные профессиональные факторы [7, 8].

Высокая заболеваемость, частые рецидивы, длительная нетрудоспособность больных, значительные экономические потери - все это даёт основания выделить язвенную болезнь, как наиболее актуальную медико-социальную проблему [8].

ЦЕЛЬ ИССЛЕДОВАНИЯ

Целью нашего исследования было изучить силу влияния основных факторов риска возникновения, неблагоприятного течения язвенной болезни желудка и двенадцатиперстной кишки для последующего обоснования необходимости усовершенствования организации медицинской помощи таким больным.

МАТЕРИАЛЫ И МЕТОДЫ

Материалами изучения были данные выкопировки с отчетных форм: «Отчет о заболеваниях зарегистрированных у больных, которые проживают в районе обслуживания лечебно-профилактического учреждения» (форма № 12, n = 136); «Отчет лечебно-профилактического учреждения» (форма № 20, n = 136); медицинские карты стационарного больного (форма 003/0, n = 400); медицинские карты амбулаторного больного (форма 025/0, n = 400), карты больных, которые выбыли из стационара (форма 066/0, всего n = 700, из них 400 - с язвенной болезнью, 300 - референтная группа (без язвенной болезни), опросные анкеты (опросник Фагестрема, GAGE, ШШТД, самооценки уровня тревожности по шкале С.Спилберга). Сформированы группы риска с 12 модифицированных (4) и немодифицированных (8) факторов, каждый из которых имеет свои признаки, градации, позволяет детализировать значение при персонифицированном подходе к формированию отдельных групп.

Сформирована компьютерная база данных в программе Microsoft Excel 2010, где массив данных сгруппирован за следующими параметрами: место жительства (городские, сельские жители), пол (мужчины, женщины) и возраст. Статистическая обработка полученного материала проведена путем расчета критерия χ^2 -квадрат Пирсона, t-критерию Стьюдента, индекса Чарлсона.

Генеральная совокупность представлена 700 пациентами, большинство из них в трудоспособном возрасте, а именно: до 60 лет - 343 (85,8%), старше 60 (14,2%). При этом, стоит отметить достоверное преимущество пациентов в по возрастной структуре до 40 лет, на долю которых приходилось 184 из 400 (46,0±2,5%) лиц. Среди общего количества больных достоверно больше было мужчин - 216 (54,0±2,5%), на женщин приходилось - 46,0±2,5% (184 лица). Представлены данные совпадают с данными литературы. Обращает на себя внимание разногласие распределения мужчин и женщин по возрасту. Среди первых - достоверно больше до 30 лет (36,1±3,3% к 22,8±3,0% среди женщин), тогда как среди вторых - в возрасте 40 - 49 лет (27,7±3,3% к 14,4±2,3% мужчин). За результатами сравнительного анализа прослеживается одинаковый состав пациентов в референтной группе.

Осуществлена количественная оценка факторов, их признаков в виде баллов, по результатам которой определено наиболее информативно значимые.

Полученные таким образом данные были обработаны, что позволило установить информационную

значимость каждого признака того или иного фактора.

Методы исследования: 1) системного подхода и анализа – для проведения комплексного исследования объекта, предмета, характера их процессов в системной взаимосвязи, а также для анализа проблемных вопросов и путей их решения; 2) социологический (анкетного опроса) – для сбора данных относительно индивидуальных факторов риска, самооценки психологически-эмоционального состояния пациентов с язвенной болезнью желудка и двенадцатиперстной кишки; 3) медико-статистический – для определения объема наблюдений, сбора, обработки и анализа полученной информации, оценки достоверности результатов исследования.

РЕЗУЛЬТАТЫ И ИХ ОБСУЖДЕНИЕ

Результаты анализа мирового и отечественного информационного контента по исследуемой проблеме засвидетельствовали наличие ряда нерешённых вопросов, в том числе влияние факторов риска на возникновение и неблагоприятное течение язвенной болезни.

Определённые нами модифицированные и немодифицированные факторы хорошо известны, перечень их согласовывается с данными литературы. Установленная информационная значимость каждого признака того или иного фактора стала основой в последующей работе по разработке прогностической таблицы с целью распределения больных ЯБ по характеру вероятности течения заболевания.

Количественная оценка качественных показателей представлена в виде баллов в таблице I.

В таблице I с немодифицированных предикторов выделяются: пол, возраст, наследственность, группа крови 0 (I) Rh+. По значимости к неблагоприятным факторам развития ЯБ относятся больные мужского пола (+2,3 балла); наиболее уязвимым является возраст до 29 лет (+2,5 балла) и 40 - 49 лет (+1,1 балла), практически вдвое меньший риск среди 50 – 59-летних пациентов.

Наследственная отягощённость у больных оценивается в 2,3 балла и по величине показателя близка к информационной ценности предыдущих факторов. Несколько меньше она у больных с группой крови 0 (I) Rh+ (+1,4 балла). Таким образом, полученные сведения совпадают с данными литературы. Они подтверждают наличие риска развития ЯБ у мужчин трудоспособного возраста, склонность передачи наследственности по мужской линии и у лиц с 0 (I) Rh + группой крови. Указанное уже само по себе свидетельствует о социальном аспекте вопроса, который должен учитываться при оказании медицинской помощи населению и проведении профилактической работы.

Однако, более весомыми, чем немодифицированные, оказались модифицированные факторы. Как оказалось, определяющим фактором является инфекция *Helicobacter pylori*, как предиктор усиления агрессив-

ности, информационный риск которого составил 9,7 баллов. Эрадикация микроорганизма не только приводит к заживлению язв, предупреждает рецидивирование, но и при минимизации степени обсемененности позволяет предупредить развитие болезни.

Вторым по значимости негативного воздействия и информационной значимости в развитии ЯБ является наличие сопутствующей патологии (+5,0 баллов). Наиболее весомыми среди других оказались болезни пищеварительной системы, особенно в случаях нарушения гастродуоденальной моторики, и гипертоническая болезнь (+3,8 и +4,0 балла соответственно). К влиятельным негативным факторам следует отнести сахарный диабет (+1,3 балла), воспалительные заболевания других органов и систем (+1,2 балла); на цереброваскулярную патологию и болезни дыхательной системы приходится по +1,0 балла. Сопутствующая патология имеет не только медицинское значение вопроса, но и его социальный аспект. Выявлено, что достоверное большинство пациентов, имея сопутствующую патологию, находилось в трудоспособном возрасте ($54,8 \pm 2,4\%$ против $45,2 \pm 2,4\%$), и становится очевидной актуальность проблемы профилактики ЯБ, особенно с точки зрения минимизации воздействия на этот процесс других болезней, что реально возможно в случае мультидисциплинарного подхода. Актуальность вопроса возрастает, учитывая наличие нескольких сопутствующих заболеваний у пациента. Так, у каждого третьего их было два, пятого - три.

При оценке влияния сопутствующей патологии, отдельным пунктом следует выделить нервно-психическое состояние, которое в настоящее время считается одним из неспецифических вредных факторов. По результатам расчетов значение фактора составило 3,0 балла. То есть подтверждено, что у больных на ЯБ превалирует соматизированный характер изменений психоэмоционального состояния.

Нарушение режима питания оказалось достаточно значимым в аспекте развития ЯБ (+3,7 балла). Практически, ему принадлежит третье место по балльной оценке после инфицированности *H. pylori* и наличия сопутствующей патологии. Этот фактор нельзя игнорировать, он подчеркивает целесообразность индивидуального подхода к пищевому рациону. С вредных привычек более значительным, чем действие алкоголя, оказалось курение (+2,5 и +3,2 баллов соответственно). Негативное влияние последнего связано с ишемией и прямым цитотоксическим эффектом на слизистую оболочку желудка.

Ситуация осложняется и доказанной информацией о негативной роли отдельных групп препаратов в плане развития острых эрозивно-язвенных поражений слизистой оболочки желудка. По результатам проведенных расчетов, информационная ценность влияния лекарств (нестероидные противовоспалительные (аспирин, индометацин и др.), кортикостероиды, антибактериальные средства, дигоксин, теofilлин, резерпин, препараты железа, калия и т. д.) оказалась

Таблица I. Факторы риска язвенной болезни

№	Фактор	Признак	Всего	без ЯБ		больные с ЯБ		m	m ²	балл
				абс	%	абс.	%			
Немодифицированные										
1.	Пол	мужчины	336	120	35,7	216	64,3	2,6	6,76	+2,3
		женщины	364	180	49,5	184	50,5	2,7	6,9	-2,3
2.	Возраст	до 29	180	60	33,3	120	66,7	3,4	11,7	+2,5
		30 - 39	133	69	51,9	64	48,1	4,3	18,6	-1,9
		40 - 49	132	50	37,9	82	62,1	4,2	17,7	+1,1
		50 - 59	128	51	39,8	77	60,2	4,3	18,6	+0,6
		60 - 69	97	54	55,7	43	44,3	5,0	25,0	-2,3
		≥ 70	30	16	53,3	14	46,7	9,1	82,8	-1,1
3.	Наследственность по ЯБ	да	198	73	36,9	125	63,1	3,4	11,7	+2,3
		нет	502	227	45,2	275	54,8	2,2	4,8	-0,8
4.	Группа крови	O (I) Rh+	393	153	38,9	240	61,1	2,4	5,8	+1,4
		другие	307	147	47,9	160	52,1	2,8	8,0	-1,5
Модифицированные										
5.	Режим питания нарушен	да	373	119	31,9	254	68,1	2,4	5,8	+3,7
		нет	307	147	47,9	160	52,1	2,8	8,0	-1,5
6.	Злоупотребле-ние алкоголем	да	270	94	34,8	176	65,2	2,8	8,0	+2,5
		нет	430	206	48,0	224	52,0	2,4	5,8	-1,7
7.	Курение	≥ 5	315	104	33,0	211	67,0	2,6	6,8	+3,2
		5	210	147	70,0	63	30,0	3,2	10,1	-7,3
		не курят	175	132	75,4	43	24,6	3,2	10,4	-8,7
8.	Сопутствующая патология	да	364	103	28,3	261	71,7	2,4	5,7	+5,0
		нет	336	197	58,6	139	41,4	2,6	7,0	-0,5
	Болезни гепатобилиарной системы	да	263	79	30,0	184	70,0	2,8	7,9	+3,8
		нет	437	221	50,6	216	49,4	2,4	5,7	-2,5
	Гипертоничес-кая болезнь	да	173	48	27,7	125	72,3	3,4	11,5	+4,0
		нет	527	252	47,8	275	52,2	2,2	4,8	-1,6
	Цереброваску-лярная патология	да	173	67	38,7	106	61,3	3,7	13,6	+1,0
		нет	527	233	44,2	294	55,8	2,2	4,7	-0,5
	Болезни дыхательной системы	да	62	23	37,0	39	63,0	6,1	37,2	+1,0
		нет	638	277	43,4	361	56,6	1,9	3,5	-0,2
	Сахарный диабет	да	31	10	32,3	21	61,7	8,3	69,7	+1,3
		нет	669	290	43,3	379	56,7	1,9	3,5	-0,1
	Воспалитель-ные болезни других органов и систем	да	224	66	29,4	138	61,6	3,2	10,4	+1,2
		нет	476	214	45,0	262	55,0	2,3	5,2	-0,5
9.	Наличие H. Pylori	да	320	54	16,8	266	83,2	2,0	4,0	+9,7
		нет	380	246	64,7	134	35,3	2,5	4,9	-7,8
10.	Нервно- психическое состояние	да	315	104	32,0	211	67,0	2,6	6,9	+3,0
		нет	385	196	51,0	189	49,0	2,5	6,4	-2,5
11.	Влияние лекарств	да	180	68	37,8	112	62,2	3,6	13,0	+1,3
		нет	520	232	44,6	288	55,4	2,2	4,7	-0,6
12.	Самолечение	да	412	147	35,7	265	64,3	2,4	5,4	+2,4
		нет	288	153	53,1	135	46,9	2,9	8,4	-3,0

средней по величине показателя (+ 1,3 балла). Важным на сегодня есть вопрос самолечения больных, отрицательное значение бесконтрольного приема лекарств по информативной значимости достигает 2,4 балла. Эти данные подтверждают необходимость комплексного подхода и указывают на пути совершенствования просветительской деятельности, как составляющей профилактической работы.

Установлена линейная зависимость между наличием факторов риска и потребностью в получении специализированной помощи. Это проявляется в длительности и кратности лечения на протяжении года в гастроэнтерологическом стационаре.

Обоснована необходимость усовершенствования организации медицинской помощи больным с язвенной болезнью в направлении реализации активно-конструктивной профилактики её возникновения.

ВЫВОДЫ

1. Сформированы группы риска возникновения и неблагоприятного течения ЯБЖ и ЯБДПК, к которым относятся 12 наиболее значимых модифицированных и немодифицированных факторов (пол, возраст, наследственность по ЯБ, группа крови, режим питания, злоупотребление алкоголем, курение, сопутствующая патология, наличие *H. pylori*, нервно-психологическое состояние, влияние лекарств, самолечение).
2. По результатам осуществления количественной оценки факторов, их признаков в виде баллов, наиболее информационно значимыми оказались наличие инфицирования *H. pylori*, сопутствующей патологии, значение которой возрастает с числен-

ностью болезней, а также нерациональный режим питания; следующие два места принадлежали курению и стрессу.

3. Доказана прямая зависимость между наличием ведущих факторов риска развития язвенной болезни, неблагоприятного ее течения и потребностью в медицинской помощи в виде длительности и кратности лечения.

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Прислана: 28. 09. 2017

Утверждена: 20. 02. 2018

HEALTH OF OPHTHALMOLOGISTS AS A PREREQUISITE OF QUALITY MEDICAL SERVICES

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ABSTRACT

Introduction: The effectiveness and efficiency of the medical sector workforce directly depend on health of medical professionals. Scientific literature pays considerable attention to the health of surgeons, physicians, obstetricians, gynecologists, infectionists and dentists paying very little, if any, attention to health problems of ophthalmologists. This study is intended to bridge this gap.

The aim at revealing the current situation and characteristics of health status of ophthalmologists using the results of sociological research and identifying health problems of the respondents in order to determine reliable preventive measures.

Materials and methods: The authors used bibliographic, medical-statistical, sociological and informational-analytical methods as well as analyzed questionnaires of the sociological survey conducted among ophthalmologists from various regions of Ukraine.

Results: The results of the sociological survey allowed determining the main medical-demographic and occupational characteristics of the ophthalmologists working at health facilities. It was found that 11,1±2,1 per 100 respondents assess their health condition as very good and 34,3±3,2 per 100 respondents - as good. At the same time every third respondent reports own health condition as satisfactory, 18,5±2,6 per 100 respondents report their health condition as bad and 2,8±1,2 per 100 respondents - as very bad. Chronic diseases in the history were confirmed by 52,8±3,4 per 100 ophthalmologists, recurrent acute diseases were reported by 48,6±3,4 per 100 respondents. Some ophthalmologists reported their low medical activity due to a number of reasons.

The main factors that adversely affect the health of ophthalmologists include considerable workload, the need to work part-time for subsistence, neuro-emotional stress, insufficiently equipped medical and diagnostic process lacking modern technologies, poor team atmosphere, lack of comfort at the workplace and others.

Conclusions: Own health condition assessed by ophthalmologists, the prevalence of chronic and acute pathology, factors of the working environment affecting health serve as the ground for improving prophylaxis activities among ophthalmologists and strengthening their health as a prerequisite for the quality medical services.

KEY WORDS: ophthalmologists, sociological research, health condition according to self-assessment data, prevalence of diseases.

Wiad Lek 2018, 71, 1 cz. II, 165-167

INTRODUCTION

Health care provision to population requires a number of prerequisites. It is known that according to the Donabedian model the quality of the result can be drawn from maintaining the quality of structure and the quality of technology [1-2]. Appropriate resource provision, human resource in the first place, is important among performance measures of the structure. In their turn effectiveness and efficiency of the medical sector workforce directly depends on health condition of medical professionals. It is proved that good health of medical professionals facilitates them in appropriate performance of their professional functions, thereby increasing their productivity on the whole. On the contrary, poor health condition of doctors decreases performance and adversely affects quality of medical care and patients' health.

It is known that the health care activities require considerable intellectual and physical efforts, endurance and alertness. Scientific research demonstrates that the work of health professionals is characterized by considerable nervous, mental and physical stress often with lack of

information for appropriate decision-making. It is associated with big responsibility, stress situations, occupational harms and infection risks [3-5].

Analysis of health status of various health professionals shows a wide range of health impairments resulting in high levels of disease incidence including occupational illnesses, chronic pathologies, inadequate self-assessment of own health condition, the need in outpatient and inpatient treatment, and other negative characteristics. According to the research data, one fourth of the respondents have chronic diseases, however less than half of them are in regular medical care. Diseases of respiratory system prevail in disease distribution of referrals to the doctors. Diseases of blood circulation system, osteodermomuscular system and connective tissue, eyes and their appendages, the digestive apparatus and genitourinary system prevail among chronic pathologies. Only one fourth of the doctors-respondents assess their health as very good and good [6-8].

Infection diseases caused by unfavorable epidemiological situation, numerous exposures to patients with infection diseases, poorly equipped health facilities, shortages of personal protection means and others are serious challenges for health of the medical staff. Tuberculosis and hepatitis prevail among occupational infection diseases [9-12].

Scientific sources present the findings of the researches of health status among various health professionals including surgeons, obstetricians, gynecologists, physicians, infectionists, phthysiologists, otolaryngologists, dentists and other specialties [13-15]. However, researching information in the scientific literature shows that the situation with health status of ophthalmologists is not studied properly.

With this in mind, we have all grounds to consider that analysis of health condition of ophthalmologists including the contributing factors is one of the effective methods for providing sound preventive services, which will eventually facilitate improvement of health status of doctors and nurses including improvements in their performance and in quality of medical services to the population.

The need to identify current characteristics of health status of ophthalmologists grows with the magnitude of visual impairment, rapid rates of eye disease rising among population and negative tendencies of its acceleration, which condition considerable workload on eye specialists.

Considering the above, the aim of this work is to reveal modern trends in health condition of ophthalmologists using the sociological research findings related to health problems in order to justify the needed preventive measures.

Focus of this research corresponds to the Action Plan Framework "Universal eye health: a global action plan 2014-2019" in the WHO European region associated with medical staff capacity growing [16].

THE AIM

The objective of the study was to reveal health status of ophthalmologists using national and foreign scientific publications, to develop research tools and to conduct sociological survey of ophthalmologists concerning their health status, influence of occupational factors on health, self assessment of health condition etc.

MATERIALS AND METHODS

The research methodology provided the use of bibliographic, medical statistics, sociological and information-analytical methods. For achieving the objective of the study and revealing the health problems in ophthalmologists including their needs the authors developed a toolkit for attitude and opinion survey of ophthalmologists. The survey program included demographic and professional characteristics of the respondents, current health problems and health self-assessment.

RESULTS AND DISCUSSION

The surveyed group provided demographic characteristics, including age and gender. Among respondents specialists

under 30 years accounted for $13,8 \pm 2,3$ per 100 respondents, from 30 to 39 years inclusive $-22,0 \pm 2,8$ per 100 respondents, from 40 to 49 years inclusive $-23,9 \pm 2,9$ per 100 respondents, from 50 to 59 years inclusive $-21,1 \pm 2,8$ per 100 respondents, older than 60 years $-19,3 \pm 2,7$ per 100 respondents.

Gender composition of the sample shows predominance of women with $56,9 \pm 3,4$ per 100 respondents as compared to men with $43,9 \pm 3,4$ per 100 respondents.

Specialists of the set sample work mostly at the health facilities in the urban area. For example, $32,1 \pm 3,2$ per 100 respondents live and work in the oblast capital, $47,2 \pm 3,4$ per 100 respondents in the towns and $20,8 \pm 2,3$ per 100 respondents in the rural area.

Formation of many professional opinions is affected by the length of work and qualification category. The survey was conducted among specialists with following lengths of work - under 5 years $13,0 \pm 2,3$ (per 100 respondents), from 5 to 9 years inclusive ($21,0 \pm 2,9$ per 100 respondents), from 10 to 14 years inclusive ($24,0 \pm 3,0$ per 100 respondents), from 15 to 19 years inclusive ($20,0 \pm 2,8$ per 100 respondents), above 20 years ($22,0 \pm 2,9$ per 100 respondents).

Survey questionnaire also included a question about material standing of the respondents. The sample provided only $5,7 \pm 2,1$ well off individuals per 100 respondents. Furthermore, most surveyed ophthalmologists assess their material standing as comfortably off, ($33,0 \pm 3,2$ per 100 respondents - as low income, $9,4 \pm 2,0$ per 100 respondents - as disadvantaged).

Opinions of ophthalmologists about their health status are of particular interest. In the course of the study it was established that $11,1 \pm 2,1$ per 100 respondents assess their health as very good, $34,3 \pm 3,2$ per 100 - as good. At the same time every third respondent reports own health condition as satisfactory ($33,3 \pm 3,2$ per 100), $18,5 \pm 2,6$ respondents report their health condition as bad and $2,8 \pm 1,2$ per 100 respondents - as very bad. The presented data show that though more than half of the respondents assess their health condition as good, one fourth of them tend to assess health as satisfactory, while $21,3 \pm 2,8$ per 100 respondents consider it bad or very bad.

Chronic diseases in the history are confirmed by $52,8 \pm 3,4$ per 100 respondents, recurrent acute diseases are reported by $48,6 \pm 3,4$ per 100 respondents.

The structure of chronic diseases shows the following pattern: 27,8% falls under diseases of the respiratory system, 15,2% - diseases of digestive system, 10,6% - diseases of blood circulatory system 9,6% - diseases of genitourinary system and 10,2% - diseases of osteodermomuscular system and connective tissue.

What is alarming is that ophthalmologists do not always consult a GP or a relevant medical specialist about diseases they suffer and their exacerbation. Only $40,6 \pm 3,4$ per 100 respondents confirmed their referral to the medical specialist for treatment. At the same time about half of the respondents ($48,6 \pm 3,4$ per 100 respondents) admitted self-treatment, shortage of time, big workload, lack of substitute specialists, light diseases symptoms etc. Insufficient attention to own health problems by a part of ophthalmologists is a negative predictive value towards potential development of diseases and deterioration of health in the future.

Among major factors adversely affecting health of ophthalmologists most of the respondents reported considerable workload (38,5±3,3 per 100 respondents), the need to work part-time for subsistence (36,4±3,3 per 100 respondents), neuro-emotional stress (33,3±3,2 per 100 respondents), insufficiently equipped medical and diagnostic process lacking modern technologies (39,8±3,3 per 100 respondents), poor team atmosphere (6,9±1,7 per 100 respondents), lack of comfort at the workplace (18,2±2,7 per 100 respondents) and others.

The revealed characteristics of health of ophthalmologists, factors adversely affecting the health condition, lack of attention to own health problems should be taken into consideration in development of the reliable prevention programs.

CONCLUSIONS

In order to provide high quality and accessible eye care system for population it is of paramount importance to provide appropriate resources to support diagnosis and treatment process, where eye medical staff plays the major role. Efficiency and effectiveness of ophthalmologists' performance directly depend on their health status.

The sociological survey of the ophthalmologists with a help of the specially developed the toolkit, which allowed learning their opinion about own health, its deterioration and contributing factors of the working environment.

The survey findings show that most ophthalmologists working at the health facilities are women, mostly in rural area, ranging from young to pension age, with various lengths of service. At the same time, every fifth employee has a retirement age, which, with a small proportion of young specialists in the structure of specialists in the ophthalmologic service, may show a unfavorable proposal for staffing in ophthalmological domain of medical care in the future. Despite the fact that more than half of respondents assess their material condition as good, one third of respondents consider themselves insufficiently secured, and every tenth is low-income, more than one third of the respondents have to work part-time for subsistence.

According to the health self-assessment data, 45 per 100 of the respondents consider it good or very good. At the same time one third of the respondents assess it as satisfactory and more than every fifth - as bad. The reason for low self-assessment is in the chronic diseases indicated by almost half of the respondents. Diseases of the respiratory system, the digestive apparatus, the blood circulatory system, the genitourinary system and the osteodermomuscular system and connective tissue prevail in the structure of chronic diseases.

Unfavorable occupational factors, which adversely affect health of ophthalmologists serve a negative predictive value towards potential development of diseases and deterioration of health in the future.

Multiple information on health of ophthalmologists and influence of the occupational factors are the ground for planning actions to prevent adversities, manage health disorders of ophthalmologists for strengthening their health, which is a prerequisite for quality performance of medical staff.

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Received: 20.10.2017

Accepted: 25.01.2018

ОСОБЕННОСТИ МЕСТНОГО ИММУНИТЕТА ПРИ ЛОКАЛЬНОЙ ВОСПАЛИТЕЛЬНОЙ РЕАКЦИИ У БЕРЕМЕННЫХ В ЗАВИСИМОСТИ ОТ РЕАЛИЗАЦИИ ВНУТРИУТРОБНОЙ ИНФЕКЦИИ

FEATURES OF LOCAL IMMUNITY IN LOCAL INFLAMMATORY REACTIONS IN PREGNANT, DEPENDING ON THE IMPLEMENTATION OF INTRAUTERINE INFECTION

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ХАРЬКОВСКИЙ НАЦИОНАЛЬНЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ, ХАРЬКОВ, УКРАИНА

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РЕЗЮМЕ

Актуальность: Вагинальные защитные системы функционируют независимо от других, системных, механизмов, и нарушения местных иммунных механизмов слизистой оболочки влагалища являются причиной инфекционной патологии репродуктивной системы

Цель: Оценить особенности местного иммунитета при локальной воспалительной реакции у беременных в зависимости от реализации внутриутробной инфекции.

Материалы и методы: 1 группа беременных женщин с наличием бактериальных инфекций с и без реализации ВУИ, 2 группа - с наличием вирусных инфекций с и без реализации ВУИ, 3 группа - с наличием инфекций сочетанной полиэтиологической структуры с и без реализации ВУИ, контрольная группа – беременные женщины с физиологическим течением беременности. Оценивали количество лейкоцитов в содержимом влагалища, концентрацию IgA, IgM, IgG, sIgA, концентрацию цитокинов – ИЛ-1 β , ИЛ-6, ИЛ-10, TNF- α в вагинальных смывах.

Результаты: У женщин с наличием инфекционного процесса без его реализации независимо от этиологического фактора отмечали более выраженные воспалительные реакции. При наличии вирусной инфекции изменения в гуморальном звене локального иммунитета менее выражены. В 1 группе без реализации ВУИ концентрация ИЛ-1 β - (73,68 \pm 10,23) пг/мл, ИЛ-6 – (53,3 \pm 6,8) пг/мл. Во 2 группе с реализацией ВУИ концентрация ИЛ-10 - (26,72 \pm 4,35) пг/мл. Во 2 группе без реализации ВУИ содержание TNF- α – (575,25 \pm 69,03) пг/мл.

Выводы: Выявлены отличия между группами беременных с различным исходом ВУИ в содержании провоспалительных и противовоспалительных цитокинов.

КЛЮЧЕВЫЕ СЛОВА: внутриутробное инфицирование, инфекционный процесс, местный иммунитет, локальная воспалительная реакция.

ABSTRACT

Introduction: Vaginal protective systems function independently of other systemic mechanisms and impairments of local immune mechanisms of the vaginal mucosa are the cause of infectious disorders of the reproductive system

The aim: To assess characteristics of local immunity in local inflammatory reactions in pregnant, depending on the implementation of intrauterine infection.

Materials and methods: The study comprised Group 1 of pregnant women with the presence of bacterial infections with and without implementation of IUI, Group 2 with the presence of viral infections with and without implementation of IUI, Group 3 with the presence of infections of combined polyetiological structure with and without implementation of IUI and control group included pregnant women with physiological pregnancy. The study implied evaluation of the number of leukocytes in vaginal contents, concentration of IgA, IgM, IgG, sIgA, concentration of cytokines-IL-1 β , IL-6, IL-10, TNF- α in vaginal swabs.

Results: Women with the presence of an infectious process without its implementation, regardless of the etiologic factor, were found to have more expressed inflammatory reactions. In the presence of a viral infection, changes in the humoral link of local immunity were less expressed. In Group 1 without implementation of IUI, the concentration of IL-1 β was (73.68 \pm 10.23) pg / ml, IL-6 was (53.3 \pm 6.8) pg / ml. In Group 2 with implementation of IUI, concentration of IL-10 was (26.72 \pm 4.35) pg / ml. In Group 2 without implementation of IUI, the content of TNF- α was (575.25 \pm 69.03) pg / ml.

Conclusions: The study showed the differences between the groups of pregnant women with different outcome of IUI in the content of proinflammatory and anti-inflammatory cytokines.

KEY WORDS: intrauterine infection, infectious process, local immunity, local inflammatory reaction.

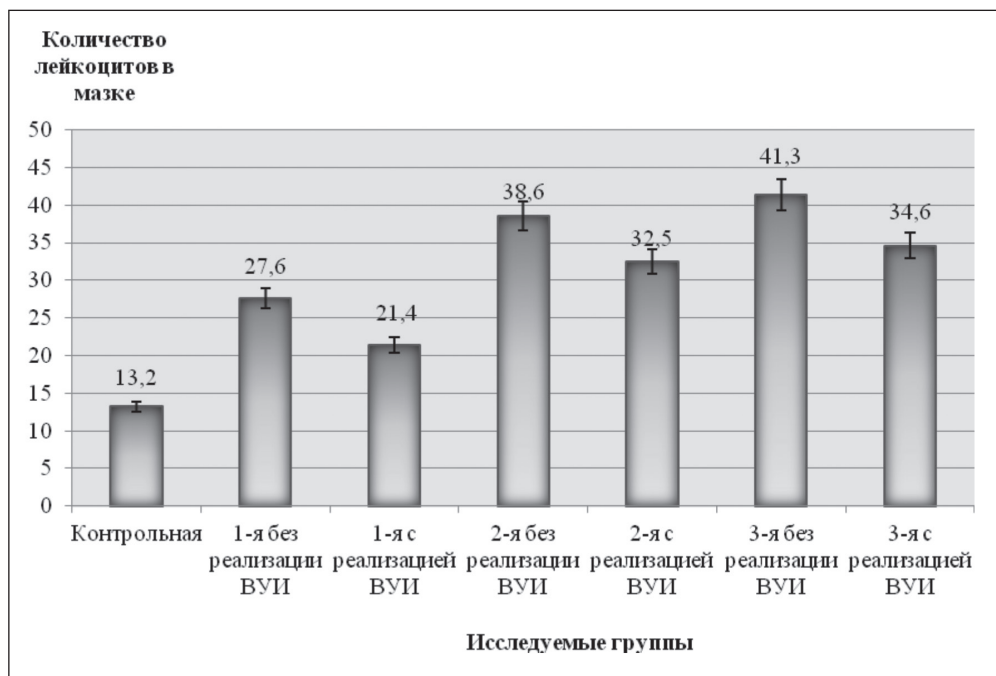


Рис.1. Количество лейкоцитов в мазках женщин исследуемых групп

ВВЕДЕНИЕ

Инфекционная патология является на сегодняшний день наиболее актуальной проблемой в акушерстве и перинатологии. Следствием, а возможно и причиной этого является снижение иммунологической реактивности организма. Авторы большинства работ, посвященных проблеме инфекционно-осложненного течения беременности, указывают на отсутствие у больных существенных нарушений системного иммунитета и преобладание в патогенезе заболевания нарушений локальных факторов противоинфекционной защиты [1,2,3].

Внимание исследователей привлекает оценка локального иммунитета, что по мнению некоторых ученых в большей степени отражает истинное состояние иммунной системы. Существует мнение, что вагинальные защитные системы функционируют независимо от других, системных, механизмов, и нарушения местных иммунных механизмов слизистой оболочки влагалища являются причиной инфекционной патологии репродуктивной системы. [4,5,6,7,8].

В слизистых оболочках сосредоточены клеточные и гуморальные факторы локальной иммунной защиты. Важная роль в поддержке местного иммунитета принадлежит иммуноглобулинам IgA, IgM, IgG, которые определяются в вагинальном содержимом, однако основная роль в противоинфекционной защите принадлежит секреторному иммуноглобулину А, который образуется лимфоидными В-лимфоцитами, располагающимися в железистом эпителии слизистых. Кроме того, в последние годы, учитывая значение, которое придают локальному иммунитету, все большее внимание уделяется исследованию цитокинового профиля во влагалище для диагностики, мониторинга и прогноза течения урогенитальных инфекций. [9,10].

ЦЕЛЬ ИССЛЕДОВАНИЯ

Оценить особенности местного иммунитета при локальной воспалительной реакции у беременных в зависимости от реализации внутриутробной инфекции.

МАТЕРИАЛЫ И МЕТОДЫ

Учитывая исход внутриутробной инфекции (ВУИ) для новорожденных, в соответствии с результатами дообследования беременных, все женщины были разделены на группы:

- 1 группа беременных женщин с наличием бактериальных инфекций без реализации ВУИ (n=30) и с реализацией ВУИ (n=30).
- 2 группа беременных женщин с наличием вирусных инфекций, без реализации ВУИ (n=30) и с реализацией ВУИ (n=30)..
- 3 группа беременных женщин с наличием инфекций сочетанной полиэтиологической структуры без реализации ВУИ (n=30) и с реализацией ВУИ (n=30).

Контрольная группа – беременные женщины с физиологическим течением беременности (n=50).

Выраженность локальной воспалительной реакции оценивали по количеству лейкоцитов в поле зрения микроскопа. Для этого стерильным инструментом брали содержимое влагалища, переносили на стекло, готовили мазки, окрашивали по методу Грама, микроскопировали, используя иммерсионную систему.

Материалом для исследования было вагинальное содержимое, из которого на стекле готовили мазки и окрашивали их метиленовым синим. Затем проводили микроскопию полученных препаратов с использованием иммерсионной системы.

Таблица 1. Содержание иммуноглобулинов в вагинальных смывах женщин исследуемых групп

Исследуемые группы	Концентрация, мг/мл			
	IgA	IgM	IgG	sIgA
Контрольная	0,12±0,05	0,11±0,02	0,66±0,03	0,64±0,04
1-я без реализации ВУИ	1,12±0,08**	1,88±0,3**	1,72±0,14**	2,02±0,32**
1-я с реализацией ВУИ	0,46±0,03*	0,76±0,05*	0,72±0,11	0,41±0,07*
2-я без реализации ВУИ	0,69±0,05**	0,98±0,08**	1,58±0,18*	1,24±0,21**
2-я с реализацией ВУИ	0,33±0,02*	0,21±0,01*	1,39±0,26*	0,69±0,08
3-я без реализации ВУИ	1,36±0,07**	2,12±0,36**	1,76±0,2	3,05±0,25*
3-я с реализацией ВУИ	0,22±0,01*	0,44±0,06*	1,85±0,3*	1,39±0,14*

*различия достоверны от контроля

** - различия достоверны в группах ($p < 0,05$)

Для оценки гуморальных факторов локального иммунитета использовали вагинальные смывы, которые получали после орошения влагалища 5 мл стерильного 0,9% NaCl. После центрифугирования лаважа при 1000 об/мин в течение 5 мин. отделяли надосадочную жидкость. В собранных биосубстратах методом твердофазного иммуноферментного анализа определяли концентрацию общих иммуноглобулинов класса А, М, G и секреторного IgA (sIgA) с использованием набора реагентов производства НПЛ «Гранум». Концентрацию цитокинов – ИЛ-1 β , ИЛ-6, ИЛ-10, TNF- α проводили методом ИФА с использованием набора реагентов производства ЗАО «Вектор-Бест».

В работе использованы методы вариационной статистики с вычислением средней арифметической и ее стандартной ошибки ($M \pm SE$) с использованием параметрических (t-критерий Фишера-Стьюдента) и непараметрических (U-критерий Вилкоксона) методов. Значимыми считали различия при $p \leq 0,05$. Расчеты проводили с использованием программ Microsoft Excel и Statistica 8,0.

РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ

Проведен анализ данных микроскопического исследования мазков, полученных из слизистых оболочек влагалища, что позволило нам оценить выраженность лейкоцитарных реакций в группах беременных с различной этиологией и исходом инфекции.

У всех беременных женщин с наличием инфекции выявили в той или иной степени достоверные изменения количества лейкоцитов относительно контрольной группы. Максимальное количество лейкоцитов ($41,3 \pm 5,2$) выявлено в 3 группе женщин без реализации ВУИ с наличием инфекций сочетанной полиэтиологической структуры. Достаточно высоким ($38,6 \pm 4,4$) было число лейкоцитов в вагинальных мазках женщин 2 группы без реализации вирусной ВУИ. Наименьшее содержание лейкоцитов определялось у женщин 1 группы с реализацией бактериальной ВУИ ($21,4 \pm 1,6$). Таким образом, у женщин с наличием инфекционного

процесса без его реализации независимо от этиологического фактора отмечали более выраженные воспалительные реакции по сравнению с группами, характеризующимися наличием признаков реализации ВУИ. Это свидетельствует о более выраженной степени напряженности локального иммунитета у беременных женщин с признаками ВУИ, родивших здоровых детей.

Для оценки гуморальных факторов локального иммунитета были проанализированы результаты содержания иммуноглобулинов различных классов (IgA, IgM, IgG, sIgA) в вагинальных смывах беременных в зависимости от исхода ВУИ и этиологической структуры (табл. 1).

Как следует из результатов, концентрация иммуноглобулинов различных классов отличалась в группах с реализацией и без реализации ВУИ.

В 1 группе женщин без реализации бактериальной ВУИ концентрация исследуемых иммуноглобулинов была достоверно повышена в 2,5-4 раза относительно группы с реализацией ВУИ и относительно контроля (табл. 1). Отмечено значительное повышение содержания IgA до ($1,12 \pm 0,08$) мг/мл относительно контроля и группы сравнения, а уровень sIgA повысился до значения ($2,02 \pm 0,32$) мг/мл при контроле ($0,64 \pm 0,04$) мг/мл.

В 1 группе женщин с реализацией бактериальной внутриутробной инфекции содержание IgA и IgM было достоверно выше ($0,46 \pm 0,030$) мг/мл и ($76 \pm 0,05$) мг/мл, чем в контроле – ($0,12 \pm 0,05$) и ($0,11 \pm 0,02$) мг/мл соответственно. Однако уровень IgG в вагинальных смывах не отличался от контроля, а уровень sIgA был достоверно ниже – ($0,41 \pm 0,07$) мг/мл.

Показатели содержания иммуноглобулинов различных классов в вагинальных смывах женщин 2 группы с диагностированной вирусной инфекцией без ее реализации были также достоверно выше, чем в группе сравнения (табл. 1). Концентрация общего IgA и sIgA в группе без реализации вирусной ВУИ была вдвое выше, а IgM и IgG – в среднем в четыре раза, чем в группе с реализацией вирусной ВУИ.

Таблица II. Содержание цитокинов в вагинальных смывах женщин исследуемых групп

Исследуемые группы	Концентрация, пг/мл			
	IL-1 β	IL-6	IL-10	TNF- α
Контрольная	11,6 \pm 0,95	6,9 \pm 0,67	7,65 \pm 0,81	295,6 \pm 37,4
1-я без реализации ВУИ	73,68 \pm 10,23**	53,3 \pm 6,8	9,39 \pm 1,22	180,85 \pm 12,89*
1-я с реализацией ВУИ	58,72 \pm 4,92*	35,88 \pm 3,04*	15,89 \pm 2,43*	156,07 \pm 11,18*
2-я без реализации ВУИ	49,48 \pm 9,43	31,0 \pm 6,4	17,98 \pm 1,24	575,25 \pm 69,03*
2-я с реализацией ВУИ	40,32 \pm 5,12*	28,29 \pm 2,71*	26,72 \pm 4,35*	149,74 \pm 11,82*
3-я без реализации ВУИ	35,56 \pm 10,13	39,4 \pm 4,0	7,57 \pm 0,17	484,10 \pm 39,64*
3-я с реализацией ВУИ	30,32 \pm 5,18*	26,22 \pm 1,83*	9,88 \pm 0,58*	312,7 \pm 34,39

*различия достоверны от контроля

** - различия достоверны в группах ($p < 0,05$)

Во 2 группе с реализацией вирусной ВУИ содержание IgA, и IgM было выше, чем в контроле, но достоверно ниже, чем в группе с реализацией бактериальной ВУИ. Содержание IgG было повышенным относительно контроля, однако достоверно не отличалось от группы сравнения – 2 группы без реализации вирусной инфекции. При этом концентрация sIgA во 2 группе с реализацией вирусной ВУИ достоверно не отличалась от контрольных значений.

Что касается 3 группы обследованных с наличием инфекции полиэтиологической структуры без ее реализации для плода, то здесь на фоне двукратного повышения относительно контроля уровня IgG отмечено максимальное содержание IgM (2,12 \pm 0,36) мг/мл и sIgA (3,05 \pm 0,25) мг/мл. Концентрация общего IgA в вагинальном содержимом указанной группы также была самой высокой из всех исследованных и составила (1,36 \pm 0,07) мг/мл.

В 3 группе обследованных женщин с реализацией ВУИ сочетанной полиэтиологической структуры содержание IgA было минимальным по сравнению с другими исследуемыми группами. При этом уровень IgM был вдвое выше, чем во 2 группе женщин с реализацией вирусной ВУИ, однако в 1,7 раза ниже относительно 1 группы с реализацией бактериальной ВУИ. Содержание IgG в указанной группе было максимальным среди всех исследованных групп и составило (1,85 \pm 0,2) мг/мл. Концентрация секреторного sIgA в вагинальном секрете также была максимальной среди групп с реализацией ВУИ – (1,39 \pm 0,14) мг/мл.

Из представленных данных следует, что при наличии вирусной урогенитальной инфекции изменения в гуморальном звене локального иммунитета менее выражены, чем при бактериальной или с наличием инфекции сочетанной полиэтиологической структуры.

Для оценки локального иммунитета исследованы уровни провоспалительных и противовоспалительных цитокинов в вагинальных смывах женщин с различным исходом внутриутробного инфицирования плода, результаты которого отражены в таблице II.

Достоверное повышение цитокинов IL-1 β и IL-6 относительно контроля наблюдали у всех женщин с наличием инфекционного процесса, однако в группах сравнения выявлены отличия в зависимости от реализации инфекции и этиологического фактора (табл. II).

В 1 группе женщин с бактериальной внутриутробной инфекции без ее реализации содержание провоспалительного IL-1 β было максимальным среди всех исследуемых групп и составил (73,68 \pm 10,23) пг/мл. В группах с наличием вирусной и с ВУИ полиэтиологической структуры без реализации для плода концентрация IL-1 β была в 1,5 – 2 раза ниже – (49,48 \pm 9,43) пг/мл и (35,56 \pm 10,13) пг/мл соответственно.

В 1 группе женщин с реализацией внутриутробной инфекции, обусловленной бактериальной инфекцией, содержание IL-1 β в вагинальных секретах было повышено пятикратно относительно контроля, однако достоверно ниже, чем в 1 группе без реализации бактериальной ВУИ. При реализации вирусной ВУИ также отмечено достоверное повышение относительно контроля содержания IL-1 β (40,32 \pm 5,12) пг/мл, а в 3 группе с реализацией ВУИ полиэтиологической структуры уровень этого провоспалительного цитокина был минимальным и составил (30,32 \pm 5,18) пг/мл.

Концентрация IL-6 – была максимальной в 1 группе женщин с наличием бактериальной инфекции без ее реализации и составила (53,3 \pm 6,8) пг/мл, что достоверно выше, чем в 1 группе с реализацией ВУИ (35,88 \pm 3,04) пг/мл при контрольных значениях (6,9 \pm 0,67) пг/мл. Во 2 группе с различным исходом вирусной ВУИ также выявлено значительное повышение содержания этого стимулирующего иммунный ответ цитокина, однако отличия в подгруппах были недостоверными. В 3 группе женщин с реализацией ВУИ с наличием инфекций сочетанной полиэтиологической структуры уровень IL-6 в исследуемом материале был минимальным – (26,22 \pm 1,83) пг/мл, и достоверно ниже, чем в аналогичной группе без реализации ВУИ.

Содержание цитокина - IL-10, обладающего выраженным противовоспалительным эффектом, также отличалось в исследуемых группах. Максимальная концентрация IL-10 выявлена в группах с наличием вирусной внутриутробной инфекции, при этом в подгруппе с реализацией ВУИ его уровень составил (26,72±4,35) пг/мл на фоне (17,98±1,24) пг/мл в подгруппе с благоприятным исходом вирусной внутриутробной инфекции. При бактериальной инфекции с ее реализацией (в 1 группе) концентрация IL-10 была повышена вдвое относительно контроля, при этом в 1 и 3 группах без реализации ВУИ значение содержания IL-10 достоверно не отличалась от контрольной группы. Отличия в 3 группе с реализацией ВУИ с наличием инфекций сочетанной полиэтиологической структуры также были недостоверными как относительно контроля, так и группы сравнения.

Содержание фактора роста опухолей – альфа (TNF-α), обладающего двойным эффектом в отношении активности иммунного ответа, в 1 группе с ВУИ бактериальной этиологии был достоверно снижен относительно контрольных значений, однако в подгруппах с различным исходом бактериальной ВУИ достоверно не отличался (табл. II). Также во 2 группе с реализацией ВУИ вирусной этиологии содержание TNF-α было достоверно снижено (149,74±11,82) пг/мл относительно контроля (295,6±37,4) пг/мл. Однако, достоверных отличий в группах с реализацией ВУИ в зависимости от этиологического фактора – бактериального или вирусного, не выявлено. В 3 группе с реализацией ВУИ сочетанной полиэтиологической структуры концентрация TNF-α была достоверно выше, чем в 1 и 2 группах с реализацией ВУИ, однако эти отличия не были достоверными относительно контроля.

Максимальное содержание TNF-α выявлено в вагинальных смывах женщин 2 группы без реализации вирусной ВУИ – (575,25±69,03) пг/мл, что почти вдвое выше, чем в контроле и в 3,8 раза выше относительно 2 группы с реализацией ВУИ. В 3 группе без реализации ВУИ концентрация TNF-α также была достоверно выше значений, полученных при исследовании женщин аналогичной группы сравнения с реализацией ВУИ сочетанной полиэтиологической структуры и контрольной группы.

ВЫВОДЫ

Таким образом, выявлены существенные отличия от контроля между группами беременных с различным исходом ВУИ в содержании провоспалительных и противовоспалительных цитокинов. Содержание провоспалительного цитокина IL-1β – ключевого фактора острой фазы воспаления, стимулирующего фагоцитарные реакции, был повышен относительно контроля, однако недостаточно, о чем свидетельствуют данные, полученные в группах женщин без реализации ВУИ. Такая же тенденция отмечается относительно IL-6 – регулятора процессов антителообразования, который был ниже в

группах с реализацией ВУИ. Напротив, содержание IL-10, угнетающего функциональную активность макрофагов, в группах с реализацией ВУИ было выше, чем в аналогичных группах без реализации ВУИ. Что касается TNF-α, который может как стимулировать, так и угнетать воспалительные реакции, то наиболее выраженное его повышение отмечали в группах без реализации ВУИ вирусной и сочетанной полиэтиологической структуры. Этот факт может свидетельствовать о роли цитокина TNF-α в реализации внутриутробной инфекции.

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Прислана: 15. 09. 2017

Утверждена: 10. 01. 2018

COMPARATIVE HYGIENIC ASSESSMENT OF ACTIVE INGREDIENTS CONTENT IN THE AIR ENVIRONMENT AFTER TREATMENT OF CEREAL SPIKED CROPS BY COMBINED FUNGICIDES

PORÓWNAWCZA HIGIENICZNA OCENA ZAWARTOŚCI AKTYWNYCH SKŁADNIKÓW W POWIETRZU PO LECZENIU ZBOŻA KŁOSOWEGO PRZY POMOCY ZŁOŻONYCH FUNGICYDÓW

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ABSTRACT

Introduction: The quality of the air environment significantly affects the health of the population. Chemical plant protection products in the spring and summer time may be the main pollutants of the air environment in rural areas. Chemical plant protection products are dangerous substances of anthropogenic origin. If applying pesticides in high concentrations, the risk of poisoning by active ingredients of pesticide preparations in workers directly contacting with it increases.

The aim: Comparative hygienic assessment of active ingredients content in the air environment after treatment of cereal spiked crops by combined fungicides was the aim of the work.

Materials and methods: Active ingredients of the studied combined fungicides, samples of air, and swabs from workers' skin and stripes from overalls were materials of the research. Methods of full-scale in-field hygienic experiment, gas-liquid chromatography, high-performance liquid chromatography, as well as statistical and bibliographic methods were used in the research.

Results and conclusions: Active ingredients of the studied combined fungicides were not detected in the working zone air and atmospheric air at the levels exceeding the limits of its detection by appropriate chromatography methods. Findings confirmed the air environment safety for agricultural workers and rural population if studied combined fungicides are applied following the hygienically approved suggested application rates and in accordance of good agricultural practice rules. However the possible complex risk for workers after certain studied fungicides application may be higher than acceptable due to the elevated values for dermal effects. The complex risk was higher than acceptable in epy case of aerial spraying of both studied fungicides, meanwhile only one combination of active ingredients revealed possible risk for workers applying fungicides by rod method of cereal spiked crops treatment.

KEY WORDS: combined fungicides, air pollution, risk assessment

Wiad Lek 2018, 71, 1 cz. II, 173-178

INTRODUCTION

The quality of the air environment significantly affects the health of the population. At the same time, the impact of pollutants on health is studied more fully in urban and industrial areas, with regular monitoring [1, 2], and monitoring is not carried out on continuing basis in rural areas [3]. Chemical plant protection products in the spring and summer time may be the main pollutants of the air environment in rural areas.

Chemical plant protection products are dangerous substances of anthropogenic origin and bear not only the benefits for mankind (as a way to reduce crop losses), but can also do significant harm to the environment and human health. Its application is accompanied by inevitable air pollution, both the working zone area and the atmospheric one. If applying pesticides in high concentrations, the risk of poisoning by active ingredients (a.i.) of pesticide preparations in workers directly contacting with it increases, and air drift with airflow over long distances is also possible

carrying these substances from the crop fields to adjacent areas, which in turn can lead to air pollution in populated areas and a deterioration in public health. Taking this into account, when allowing new chemical molecules and combinations of already known a.i. in fungicides to be applied on crops detailed research should be carried out to determine the residual quantities of the a.i. in the air environment, both the working zone area and in the atmospheric air.

THE AIM

Aim of the work: comparative hygienic assessment of active ingredients content in the air environment after treatment of cereal spiked crops by combined fungicides.

Tasks of the research: 1) determine the actual levels of azoxystrobin, benzovindiflupyr, epoxiconazole, kresoxim-methyl, metalaxyl-M, propiconazole, prochloraz, tebuconazole, fludioxonil and cyproconazole in the air of the working zone, 50 m, 300 m or

Table I. Content of active ingredients in combined fungicides and the terms of pesticides application

Formulation	Active ingredient	Content of a.i. in formulation, g/l (g/kg)	Application rates for formulation, l/ha (l/t)	Application rates for treatment solution, l/ha (l/t)	Treated area, ha (amount of treated grain, t)	Number of treatments	Crops	Location of the site
Treatment of the grain and its planting								
F. №1	fludioxonil	18,75	2	10	1	1	grain of spring barley	50°13'40"N, 30°39'00"E
	cyproconazole	6,25						
F. №2	metalaxyl-M	20	1,5	10	1	1	grain of spring barley and spring wheat	49°21'7"N, 27°21'15"E
	tebuconazole	30						
Rod treatment								
F. №3	azoxystrobin	80	0,75	300	1	1	spring barley, spring and winter wheat	49°21'7"N, 27°21'15"E
	cyproconazole	200						
F. №4	epoxiconazole	75	1,5	300	1	2	spring and winter wheat	49°47'59"N, 30°00'04"E
	prochloraz	300						
F. №5	kresoxim-methyl	240	1,0	200	1	1	spring and winter wheat	49°36'29"N, 28°05'51"E
	tebuconazole	125						
F. №6	benzovindiflupyr	83,33	0,6	300	1	2	spring barley, spring and winter wheat	49°21'7"N, 27°21'15"E
	propiconazole	208,33						
	cyproconazole	66,67						
F. №7	azoxystrobin	120	1,0	300	1	2	spring barley, spring wheat	50°15'33"N, 31°09'31"E
	tebuconazole	200						
F. №8	azoxystrobin	80	2,0	300	1	2	spring barley, spring and winter wheat	50°20'24"N, 30°25'22"E
	tebuconazole	160						
Aerial spraying								
F. №3	azoxystrobin	80	0,75	100	3	1	winter barley	48°37'15"N, 25°44'15"E
	cyproconazole	200						
F. №6	benzovindiflupyr	83,33	0,6	100	3	2	winter barley	48°37'15"N, 25°44'15"E
	propiconazole	208,33						
	cyproconazole	66,67						

1000 m from the edge of the field in the treatment zone on day 0, and also in the treatment zone and at a distance of 100 m from the treatment site on days 3 and 7; 2) give a hygienic assessment of the content of azoxystrobin, benzovindiflupyr, epoxiconazole, kresoxim-methyl, metalaxyl-M, propiconazole, prochloraz, tebuconazole, fludioxonil and cyproconazole in atmospheric air and working zone air after the studied combined fungicides application.

MATERIALS AND METHODS

A.i. of the studied combined fungicides, samples of air, swabs from workers' skin and stripes from overalls were materials of the research.

Methods of full-scale in-field hygienic experiment, gas-liquid chromatography (GLC), high-performance liquid chromatography (HPLC), as well as statistical and bibliographic methods were used in the research. The studies for preparations No. 1 and 2 were carried out during the grain treatment and its planting using a PS-10 seed protectant, a disk seeder equipped with MTZ-82 tractor; for formulations (f.) No. 3, 4, 6-8 – at the rod treatment method of cereal crops spraying using MTZ-82 tractor equipped with trailed boomless sprayer OPS-2000 (Landini-2000 – for preparation No. 5); for preparations No.3 and 6 – at aviation method of crops spraying using AEROS-2 trike, equipped with a small-drop sprayer.

Table II. Meteorological conditions during the treatments

Formulation	Air temperature at the time of treatment, °C	Atmospheric pressure, mm Hg.	Relative humidity, %	Air movement speed, m/s
Treatment of the grain and its planting				
F. №1	10	755	55	1,0-2,0
F. №2	14	750	70	1,5-2,5
Rod treatment				
F. №3	19	745	70	1,0-2,0
F. №4	25	745	60	2,0
F. №5	17	750	60	1,0-1,5
F. №6	19	742	70	1,0-2,0
F. №7	20	745	60	1,0-2,0
F. №8	18	745	60	1,0-2,0
Aerial spraying				
F. №3	21	745	60	1,0-2,0
F. №6	21	745	60	1,0-2,0

Content of a.i. in the studied combined fungicides as well as the terms of pesticides application is given in the table I.

Preparation of treatment solutions and filling-in of the seed protectant, as well as sprayer tanks was carried out on specially equipped sites (solution sites) in the immediate vicinity of the treatment site, the spray tank was pre-filled with 1/3 water, then the required amount of the preparation was added, the contents of the tank were mixed with a hydraulic stirrer (rod treatment), then water was added to the required volume. The duration of the operation for the preparation of the treatment solution was 10 minutes (for all types of treatments), the duration of grain treatment and packing was 20 minutes each, the planting of the treated grain lasted 30 minutes, the processing time for cereal spiked crops treatment was 40 minutes in the rod spraying and 20 minutes at aerial spraying. All treatment works with the abovementioned preparations were carried out under the allowable meteorological conditions given in Table II.

Determination of a.i. content in air samples after grain and cereal spiked crops treatment were conducted in accordance with the «Methodological Guidelines for the Hygienic Assessment of New Pesticides», approved in Ukraine.

Samples of the materials were sampled and delivered to the laboratory in accordance with the “Uniform Rules for sampling agricultural products, food and environmental objects for the determination of micro-quantities of pesticides”. Air samples during the preparation of treatment solutions, during the treatment of grain and its packing, filling the seed protectant with treated grain and sprayers with treatment solutions, in the tractor cab and in the cockpit of the airplane, and also in the treated sites were sampled by portable two-channel electroaspirator EA-2-20. Control samples were taken from areas where the treatment was not performed.

Also, to estimate the risks of dermal and inhalation impact on workers contacting with plant protection products, while they were performing work operations, cotton fabric stripes attached to the work clothes during the period of work were sampled.

Each value of the content level in the samples was estimated as the average of the 3 samples obtained.

Three workers were involved in the process of grain treatment; when sowing grain – 2 persons; during the treatment of cereal spiked crops – 2 workers (rod treatment) and 3 workers (aerial spraying). In the course of all production operations, the workers were provided with overalls, which included: an overall of synthetic fabric and boots, gloves and a respirator (when filling the tanks or seed protectant) were used as personal protective equipment.

Determination of azoxystrobin, benzovindiflupyr, kresoxim-methyl and fludioxonil content was performed by HPLC; metalaxyl-M, propiconazole, prochloraz, tebuconazole, cyproconazole, and epoxiconazole were performed by GLC.

Limits of detection (LOD) by the above methods for the studied a.i. content in the air of the working zone and atmospheric air, as well as hygienic standards of tentatively safe exposure levels (TSEL) are given in table III.

RESULTS AND DISCUSSION

In the course of the studies it was found that the residual quantities of the a.i. of preparations Nos. 1-2 in breathing zone (b.z.) of tank loaders (the site for preparation of solutions and filling of seed protectant), in the b.z. of the seed protectant operator did not exceed the limits of detection of the methods, whereas in the b.z. of the grain bag sewing machine operator during f. No.1 application

Table III. Hygienic norms and limits of detection of the studied pesticides in the working zone air and atmospheric air

Active ingredient	Limit of detection, mg/m ³		tentatively safe exposure level, mg/m ³	
	Atmospheric air	Working zone air	Atmospheric air	Working zone air
azoxystrobin	0.001	0.001	0.01	1
benzovindiflupyr	0.0005	0.016	0.002	0.1
cyproconazole	0.008	0.05	0.01	0.1
epoxiconazole	0.0004	0,005	0.0005	0.01
fludioxonil	0.002	0.002	0.002	1
kresoxim-methyl	0.025	0.5	0.05	1
metalaxyl-M	0.008	0.25	0.01	0.5
prochloraz	0.0008	0.05	0.001	0.1
propiconazole	0.0008	0.004	0.001	0.5
tebuconazole	0.002	0.005	0.02	0.4

the concentration of fludioxonil was 0.2 mg/m³, cyproconazole – 0.05 mg/m³, f. No. 2 application – the a.i. were not detected. Concentrations of a.i. in the b.z. of seeders operators and tractor drivers did not exceed the limits of detection for the methods of determination. The level of a.i. content in the air of possible drift at a distance of 50 meters from the treated site, as well as at the leeward side edge of the field scattered by the treated grain (during the treatment/planting, on days 3 and 7 after treatment) was below the LOD.

During the studies of the air environment at the treatment of cereal spiked crops by the ground (rod) method, it was found that the a.i. residual amounts of preparations Nos. 3-8 in the b.z. of the tank loaders (the sites for the preparation of solutions and filling of rod sprayers), the b.z. of the tractor drivers, and also in the air at the zones for making the crops treatment after 1 and 3 hours, and 3 days were less than the limits of the detection of the methods. The level of a.i. content in the air of possible drift at a distance of 300 meters from the leeward side edge of the treated fields during treatment and at a distance of 100 meters on days 3 and 7 the concentration of the studied preparations a.i. was below the limits of detection of the methods.

In the course of the study of the air environment, spraying preparations on cereal crops by an aerial method, it was found that azoxystrobin (component of f. No. 3) was detected in the air of the tank loader b.z. (the treatment solution preparation site and filling) at 0.005±0.001 mg/m³. It was also found in the b.z. of the flagman at a level of 0.006±0,002 mg/m³ and in the area of the crops treatment after 1 hour at the level of 0.005±0.003 mg/m³, whereas in the pilot b.z. and in the area of the crops treatment in 3 hours ca and 3 days after was no longer detected. The second component of f. No. 3 tebuconazole at all stages of treatment and the following hours after was not detected in the air in quantities exceeding LOD. When assessing the air environment during the cereal crops treatment with the f. No. 6 the component propiconazole was found in the b.z. of the flagman at a level of 0.04±0.006 mg/m³, and also after 1 hour in the treatment zone at

0.009±0.001 mg/m³. The level of a.i. content in the air of possible drift at a distance of 1000 meters from the leeward side edge of the treated fields during treatment, after 1 and 3 hours, and at a distance of 100 meters after 3 and 7 days, the concentration of the studied preparations a.i. was below the limits of detection of the methods.

The study also determined the level of the f. No. 1-8 a.i. content in swabs from bare skin areas and stripes from the overalls of workers, since pesticides can affect the body of workers by dermal exposure together with inhalation one [4].

The following results were obtained: the f. No. 1 component - fludioxonil was found in swabs from gloves of loader and the bag sewing machine operator at 0.003 and 0.004 mg/swab, respectively, as well as in stripes from overalls in the breast region of the bag sewing machine operator at 0.002 mg/dm². The f. No.2 a.i. – tebuconazole and metalaxyl-M were detected in swabs from gloves of the loader at the level of 0.003 and 0.002 mg/swab, respectively; the f. No.3 a.i. (azoxystrobin and cyproconazole) were found in swabs from loader gloves at the level of 0.043 mg/swab and 0.01 mg/swab, as well as in the stripes from the breast and forearm at the level of 0.012 mg/dm² and 0.0057 mg/dm², respectively. Component of f. No.4 - prochloraz was found in swabs from the gloves of loader at the level of 0.007 mg/swab, as well as in stripes from the region of the chest and forearms – 0.002 mg/dm²; the f. No. 5 a.i. (kresoxim-methyl and tebuconazole) were found in swabs from the loader gloves at 0.003 mg/swab and 0.0045 mg/swab respectively, the concentration of tebuconazole was detected in the stripes from the chest and forearms region, as well as from the back and thighs of the loader at the level of 0.003 mg/dm² and 0.002 mg/dm², respectively. Component of f. No.6 – propiconazole was found in swabs from loader gloves at the level of 0.005 mg/swab; the f. No. 7 a.i. (azoxystrobin and tebuconazole) were found in swabs from loader gloves at a level of 0.013 mg/swab and 0.02 mg/swab, respectively, and also found in the stripes from the chest and forearms region of the loader at the level of 0.0011 mg/dm² and 0.002 mg/dm², respectively.

Table IV. Values of calculated risk for workers (in arbitrary units)

Formulation	combined percutaneous effect	combined inhalation effect	complex effect
№1	0,4503	0,2459	0,6962
№2	0,1617	0,2592	0,4209
№3	0,8044	0,2558	1,0602
№4	0,9885	0,6375	1,6260
№5	0,3849	0,2922	0,6771
№6	0,5036	0,2557	0,7593
№7	0,0471	0,0077	0,0548
№8	0,0628	0,1446	0,2074
№3	2,5133	0,5767	3,0900
№6	3,1871	0,9362	4,1233

The f. No.8 a.i. (azoxystrobin and tebuconazole) were found in swabs from loader gloves at levels of 0.009 mg/swab and 0.025 mg/swab, respectively, the component of the f. – tebuconazole was found in the stripes from the chest and forearms region of the loader at 0.003 mg/dm².

In the aerial spraying of cereal spiked crops by the f. No. 3, its a.i. (azoxystrobin and cyproconazole) were detected in swabs from the tank loader gloves at the level of 0.03 mg/swab and 0.007 mg/swab respectively, as well as these substances were found in the stripes from chest and forearms region of the loader and the pilot at the 0.001 mg/dm² and 0.009 mg/dm², respectively. Estimating the f. No.6 application by the aerial method, its component – propiconazole was found in swabs from loader gloves at 0.004 mg/swab, as well as in stripes from the chest and forearms region, and from the back and thighs at the level of 0.003 mg/dm² and 0.005 mg/dm², respectively.

On the basis of the obtained data on the f. Nos. 1-8 a.i. concentration in the air of the working zone, as well as in swabs from bare skin areas and stripes from overalls, we also calculated the combined and complex risks of dermal and inhalation effects, in conditions of the all work operations performance by one person, as such conditions can arise in small farms (table IV).

It was found that the combined risk of percutaneous and inhalation effects, in conditions when all the operations were performed alone, applying these combined fungicides, in the case of f. No. 3 (in rod and aerial spray treatment), f. No.4 and 6 application, the calculated risk of possible harm to workers via dermal and inhalation routes of exposure exceeded 1 arbitrary unit, but the combined effect of active substances (both the dermal and inhalation influence separately) in the conditions of the all stages of treatment work performance, was lower than 1 arbitrary unit. It should be noted that both f. No.3 applications, as by rod spraying and aerial spray treatment, were accompanied with elevated possible risk for workers.

In the case of f. No. 1, 2, 5, 7, 8 applications, the calculated risk was not exceeding 1. But it should be noted that the performance of work on the preparation of treatment

solutions of combined fungicides and its loading to the sprayers is accompanied by the highest degree of risk of harmful effects (mainly by the dermal route of exposure).

CONCLUSIONS

Based on the results of the studied fungicides content dynamics determination (azoxystrobin, benzovindiflupyr, cyproconazole, fludioxonil, epoxiconazole, kresoxim-methyl, metalaxyl-M, propiconazole, prochloraz and tebuconazole) in the air of working zone and atmospheric air during formulations application with the maximum proposed rates it was found that there is no pollution of air above developed and approved hygienic standards and the air quality is not deteriorating at time and after applications.

But the findings of above mentioned dynamics together with the detected content of active ingredients in the swabs and stripes during formulations application with the maximum proposed rates suggested that particular combinations of fungicides have possible risk of effects on the agriculture workers who applying combined fungicides for cereal spiked crops treatment. Instructions and guidelines for these combined fungicides safe application were developed by us and approved by Ministry of Health of Ukraine and accepted for the use in work of State Service of Ukraine on Food Safety and Consumers Protection. The findings should be taken into account in the programs of monitoring the labour conditions of agriculture workers using combined fungicides on cereal spiked crops.

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Received: 14.10.2017

Accepted: 02.02.2018



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**INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE,
DEVOTED TO THE WORLD HEALTH DAY 2018,
WHICH IS DEDICATED TO UNIVERSAL HEALTH COVERAGE
AND WHO 70TH ANNIVERSARY YEAR**

Dear Colleagues!

On April 5-6, 2018 the International Scientific and Practical Conference devoted to the World Health Day 2018 will take place at the Bogomolets National Medical University. In 2018 this Conference is dedicated to Universal Health Coverage and WHO 70th anniversary year. The Conference is brought in the Register of congresses, symposia, scientific conferences, which will be spent in 2018.

MAIN DIRECTIONS OF THE CONFERENCE WORK:

- Universal Health Coverage
- Current issues of prevention and treatment of depression
- Current strategies against the epidemic of noncommunicable diseases
- Peculiarities and tendencies of population health, new challenges and threats
- Development of public health service in the context of European policy "Health – 2020"
- Strengthening and reforming health systems
- Activity of medical institutions in terms of military operations and emergency situations
- Socially meaningful and socially dangerous diseases (tuberculosis, AIDS, etc.)
- Preventive strategies in public health
- Socio-economic and ecological determinants of health
- Availability and quality of health care, family medicine
- Medical and social maintenance of certain groups of population
- Evidence-based medicine
- Management in Health Care
- Health care financing
- Legal and ethic principles of health service

FORMS OF PARTICIPATION IN THE CONFERENCE

1. Oral report and publication of abstracts
2. Postal presentation and publication of abstracts
3. Publication of abstracts

WORKINGS LANGUAGES OF THE CONFERENCE: Ukrainian, Russian, English.

Registration form and all materials for participation in the Conference should have been sent by March, **18, 2018**.
On the questions related to the organization and conducting the Conference call tel. 38-044-236-42-33,
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Thanks in advance for your participation in the Conference!

CLINICAL AND LABORATORY CHARACTERISTICS OF HEPATITIS D IN REPUBLIC OF SAKHA (YAKUTIA)

CHARAKTERYSTYKA KLINICZNA I LABORATORYJNA WIRUSOWEGO ZAPALENIA WĄTROBY TYPU D W REPUBLICIE SACHA (JAKUCJA)

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ABSTRACT

Introduction: The epidemiological situation for hepatitis D has changed significantly. Reduced population authors infection due to a sharp decline in hospitalizations from Central Asia regions, the Caucasus and Moldova, which are known to be endemic for hepatitis D. Currently, the incidence of chronic hepatitis D (HGD) in Russia is 1%, while in the countries of Central Asia, and in particular in Turkmenistan, the share of HGD among chronic viral hepatitis is 8%.

The aim of research was to establish the clinical features, depending on the activity of the replication of hepatitis viruses B and D.

Materials and Methods: We studied 26 patients with viral hepatitis D with a determined activity replicative virus by PCR (polymerase chain reaction). The age of patients ranged from 28 to 78 years. The patients performed the ELISA (enzyme-linked immunosorbent assay) study for the presence of markers of parenteral viral hepatitis (HBsAg, a-HCV and a-HDV), the standard general clinical biochemical blood tests. of the instrumental methods survey used ultrasonography (ultrasound), EGD (fibrogastroduodenoscopy). Grading the severity of liver cirrhosis established by Child-Pugh (eng. Child-Pugh, Child-Turcotte, Child-Turcotte-Pugh, sometimes Child-Paquet) is designed to assess the severity of cirrhosis. The severity of liver cirrhosis is assessed on a point system, which are calculated from 5 or 6 parameters.

Results: It is established that most HGD more prevalent among young people bodied (69%) and occurs mainly in severe symptoms and portal hypertension leading to the rapid development of liver cirrhosis (53%). It showed that hyperenzymemia reaches high levels of ALT to 1715 U / L. with a high viral DNA load virus (HBV) $2648226,0 \pm 953892,7$ copies / ml in the presence of an RNA virus D (HDV +).

Conclusion: Thus, the main feature of chronic hepatitis D is its predominant tsirrognost.

KEY WORDS: chronic viral hepatitis B and D, HDV-infection, viral load, viral replication is the D, cirrhosis of the liver.

Wiad Lek 2018, 71, 1 cz. II, 179-183

INTRODUCTION

Chronic delta infection (the HDV infection) is one of the most severe and rapidly progressing liver disease with a high risk of developing cirrhosis and hepatocellular carcinoma (HCC). HBV markers D (HDV-infection) can be infected up to 5% of the patients with HBV-infection and, thus, it is believed that there are approximately 15-20 million patients with chronic hepatitis D [1,2]. The epidemiological situation for hepatitis D has changed significantly. Reduced population authors infection due to a sharp decline in hospitalizations from Central Asia regions, the Caucasus and Moldova, which are known to be endemic for hepatitis D [3]. Currently, the incidence of chronic hepatitis D (HGD) in Russia is 1%, while in the countries of Central Asia, and in particular in Turkmenistan, the share of HGD among chronic viral hepatitis is 8% [4]. According to our research we recorded a high prevalence of the HDV-infection in the Republic of Sakha (Yakutia) and its individual medical

and geographical areas: in Viluskii and arctic regions of antibody to hepatitis D (a-HDV) was determined in 14% and 9.9%, respectively, while the average for the country of 8.3% [5]. It was also demonstrated the presence of HCV II genotype D, found in 47%, even 53% determined genotype I. In European Russia (NW FD) dominates I virus genotype D (93%), whereas the virus genotype D defined II in rare cases - 7% [6]. Studies of recent years is set to determine the DNA of HBV (DNA virus) RNA and HDV (RNA virus D) for the diagnosis of viral hepatitis forecast D. Availability and degree of HDV RNA viral load of HBV DNA in the blood serum are signs of viremia, indicating both virus replication, that are associated clinically with significant inflammatory activity in the liver. The possibility of infection in patients with chronic hepatitis D other hepatitis viruses, as well as the possibility of more than 3 combined forms pointed out by many authors, and emphasize that HDV suppresses HBV replication and HCV (hepatitis C virus) [7,8].

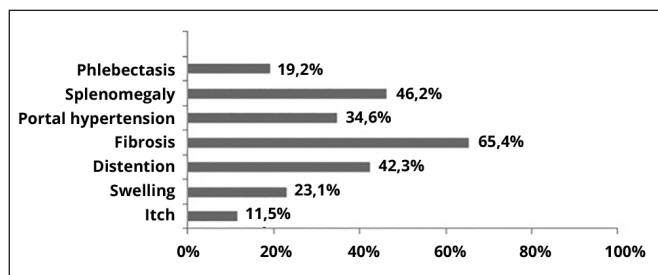


Figure 1. Frequency of clinical symptoms and syndromes in patients with chronic hepatitis D

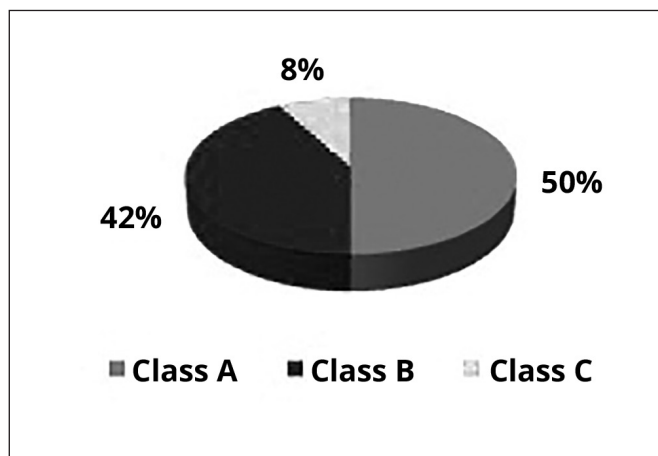


Figure 2. The severity of liver cirrhosis in all patients by grade Child-Pugh

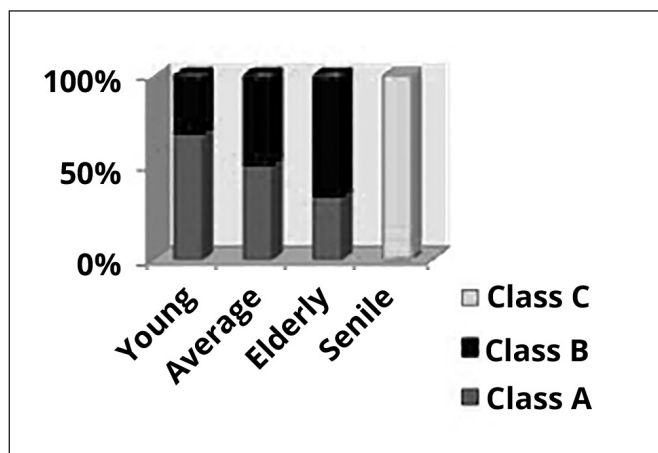


Figure 3. Distribution by grade of severity of cirrhosis by Child Social age groups

THE AIM

The aim of research was to establish the clinical features, depending on the activity of the replication of hepatitis viruses B and D.

MATERIALS AND METHODS

We studied 26 patients with viral hepatitis D with a determined activity replicative virus by PCR (polymerase

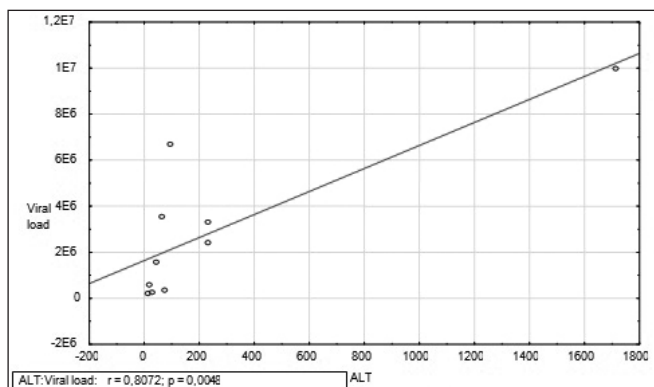


Figure 4. Indicators of ALT in patients with chronic hepatitis D with a viral load of HBV DNA and the positive RNA HDV (+)

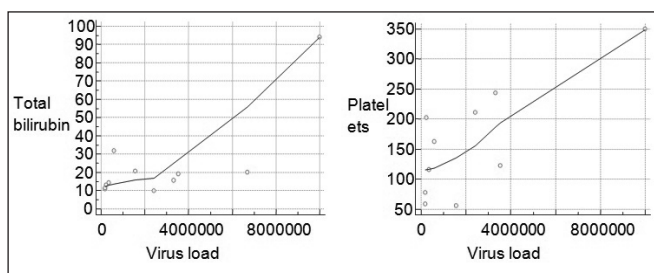


Figure 5. Dependence of total bilirubin and platelet of viral load

chain reaction). Identified viral load (VL), hepatitis B virus and hepatitis C virus the D - qualitative (presence of the virus - (+) absent - (-) All patients were hospitalized in the infectious ward for patients with viral hepatitis YAKGB for the period 2015-2016.. The age of patients ranged from 28 to 78 years (median, '41). The patients performed the ELISA (enzyme-linked immunosorbent assay) study for the presence of markers of parenteral viral hepatitis (HBsAg, a-HCV and a-HDV), the standard general clinical biochemical blood tests. of the instrumental methods survey used ultrasonography (ultrasound), EGD (fibrogastroduodenoscopy) In order to determine the severity of the clinical course of the disease evaluated the following symptoms that characterize the development of cirrhosis of the liver: flebektaziya (disruption of the normal functioning of the valves and veins of the esophagus), splenomegaly, portal hypertension, swelling of the upper and lower limbs, skin itching. Grading the severity of liver cirrhosis established by Child-Pugh (eng. Child-Pugh, Child-Turcotte, Child-Turcotte-Pugh, sometimes Child-Paquet) is designed to assess the severity of cirrhosis. The severity of liver cirrhosis is assessed on a point system, which are calculated from 5 or 6 parameters. In total there are three classes: A, B and C: Class A (Child A) - 5-6 points, Class B (Child B) - 7-9 points, Class C (Child C) - 10-15 points.

The statistical processing of the material carried out using SPSS STATISTICS 17.0 package (SPSS Inc.). Check the normality of the distribution of quantitative traits performed using the Kolmogorov criterion - Smirnov adjusted Lillieforsa criterion and Shapiro - Wilk. A comparison of independent groups by variables used Mann-Whitney,

Table I. Laboratory findings of patients with chronic hepatitis D (HDV+)

Laboratory findings	n	Average	Innaccuracy	Min	Max
Albumen	20	34,3	1,7	15,4	44,4
Points	12	6,8	0,5	5,0	11,0
The viral load (VL)	11	2648226,0	953892,7	197745,0	10000000,0
Hemoglobin	26	127,0	5,8	57,0	169,0
Iron	9	20,6	3,1	6,9	35,8
Potassium	7	4,0	0,1	3,6	4,4
Creatine	25	75,4	2,8	49,0	106,0
Urea	25	3,9	0,2	1,2	6,5
Sodium	7	139,8	0,6	138,0	142,0
Total protein	23	68,5	1,5	56,3	79,8
ESR	26	13,8	2,0	1,0	48,0
Platelets	25	136,4	14,0	56,0	350,0
Cholesterol	21	4,1	0,2	1,9	6,4
AP	23	123,8	9,3	67,0	219,0
Erythrocytes	26	4,1	0,1	1,9	5,6
	n	Median	25 - 75 P	Min	Max
ALT	26	85,0	42,8 - 177,0	13,5	1715,0
AST	26	72,3	55,4 - 115,6	19,7	1189,0
Amylase	22	31,7	26,2 - 44,8	23,0	58,5
AFP	18	10,0	5,9 - 32,0	2,7	114,3
GGT	22	120,5	47,0 - 150,0	13,0	703,0
Glucose	25	4,5	4,1 - 4,6	3,5	8,4
White blood cells	26	4,5	2,8 - 6,5	1,6	308,0
Total bilirubin	26	16,7	11,5 - 23,7	3,8	94,0
REA	18	3,9	3,1 - 5,4	0,5	354,0

Kruskal-Wallis test and analysis of variance. A comparison of the qualitative characteristics was performed using the method chetyrehpolnyh table (contingency table) with calculation of χ^2 test. Correlation analysis was used to identify and examine the relationship between quantitative traits by calculating the Pearson correlation coefficient and Spearman. The critical value of the significance level (p) is assumed to be 5%.

RESULTS AND DISCUSSION

To study the clinical manifestations of chronic hepatitis D analysis of clinical and laboratory parameters of disease in 26 patients with chronic viral hepatitis D. Among these men was 12 (46%), women - 14 (54%). Alarming situation prevailing most patients of working age. The proportion of young patients in total amounted to 69% (18-44 years of age under the new classification adopted by WHO). All patients diagnosed with chronic hepatitis D varying degrees of activity. ELISA method in these patients revealed HBsAg and total a-HDV. It should be noted that in these patients traditionally used diagnostic techniques revealed no active

replication of hepatitis B virus markers such as HbeAg, a-HBcor IgM, hepatitis D - a-HDV IgM. Only by PCR was able to detect viruses of hepatitis B and D, which indicates the importance of molecular biological research methods followed by genotyping. So, of HBV DNA was detected in 11 (42.3%), RNA HDV - in 12 (46.1%) patients, and simultaneous replication of both hepatitis B and D (mixed DNA replication and RNA HBV + HDV +) was found in 6 (23 %) patients, mono virus replication D (HDV +) in the absence of replicating virus (HBV-DNA negative) - 4 patients. Three patients were absent in serum hepatitis viruses B and D (non-replicative variant or lower detectable viral load by PCR). Of the three identified options for chronic hepatitis D (in phases mixed mono replication and non-replicative phase) the first two differ rapidly progressive course with the end result in cirrhosis of the liver. Available factual material indicates the presence of different options for chronic hepatitis current D, depending on the activity of each of the replication of viruses.

A detailed examination of clinical and laboratory parameters of disease in 26 patients with chronic hepatitis D - in terms of cytolytic syndrome (aminotransferases - ALT,

AST), viremia (HV DNA of HBV, the presence of HDV RNA) and clinical manifestations of the disease, chronic hepatitis D low activity was detected in 14 patients (53.5%), moderate to severe activity - the remaining 12 (46.5%) patients. Patients with chronic hepatitis D with moderate to severe active disease diagnosed cirrhosis. The diagnosis is justified by the presence of signs of portal hypertension patients - namely, not amenable to treatment of ascites, anasarca, peripheral edema and varicose veins in the lower third of the esophagus, identified during the gastroscopy. The most intense clinical manifestations of the disease in chronic hepatitis D (hemorrhagic, dyspeptic syndromes, telangiectasia and hepatomegaly) found exclusively in all patients. One-third - found manifestations of portal hypertension (37.3%). The most common clinical signs were forming cirrhosis due to chronic hepatitis D as liver fibrosis (62.4%), splenomegaly (42.4%), abdominal distension (41.5%), peripheral edema (22.6%), itchy skin (13.5%). Consideration of the main clinical symptoms and syndromes are shown in Figure 1.

In 12 (46.1%) of patients on the severity of signs of portal hypertension, such as the dimensions of portal vein by ultrasound indications of esophageal varices on EGD indications, degree of fibrosis (fibroscan), peripheral edema proved cirrhotic stage of chronic hepatitis D. Graduation (class) the severity of liver cirrhosis established by Child-Pugh (classes A, B, C). Half of the patients had Class A on Child Pugh (50%), 42% - Class B, 8% - Class C. This indicates that half of patients with cirrhosis of the liver proceeded relatively benign. Below, in Figures 2 and 3 shows the distribution of patients with chronic hepatitis D in the stage of liver cirrhosis by class Child Social depending on the age of the patients.

Based on the data in individuals younger cirrhosis forms more slowly and more than half of patients at the time of examination was compensation stage (Class A - 58.8%). Patients in the elderly prevailed cirrhosis of class B (78.2%), in old age, the severity of cirrhosis corresponded to Class C.

The results of laboratory parameters, especially biochemical, examined patients confirmed the well-known thesis that the main feature of viral Hepatitis D is the development of mixed-hepatitis, ie, liver under the influence of two hepatotropic virus - HBV and HDV. Supporting the role of hepatitis B virus is undeniable, but there is every reason to believe that the leading role belongs to hepatitis D. In comparison with other etiological forms of viral hepatitis, hepatitis D is more severe, as due to the influence of two viruses.

In the study of laboratory data is noteworthy that hyperenzymemia reaches from minimal to high rates - from 85.0 to ALT 1715 U / L. with a high viral load in viral DNA (HBV) - $2648226,0 \pm 953892,7$ copies / ml in the presence of an RNA virus D (HDV +). Increased bilirubin was small and moderate (Table I).

At moderate and high activity of chronic hepatitis D were significantly higher than at low, the following laboratory parameters: ALT - 148.0 vs. 42,8 (K-W = 11,9; $p = 0.0006$); AST - 108.4 vs. 55.4 ($p = 0.0006$); GGT - 136.0 vs. 45.0 ($p = 0.001$). There is a clear dependence on the degree of

increase of ALT in viral load: the higher the viral load, the higher the cytolysis of liver cells, confirming the direct effect of cytolytic viruses B and D - $\rho = 0,8$; $p = 0.0048$ (all patients HDV RNA positive) (Figure 4).

The viral load in patients with highly active chronic hepatitis D was also higher - 3434238.0 against 420,980.5 ($p = 0.01$). And in males indicators of liver enzymes were higher than those of women: AST - 94.7 vs. 55.4 ($p = 0.007$); ALT - 149.7 vs. 29.4 ($p = 0.0005$); GGT - 127.0 vs. 58.0 ($p = 0.008$). Increased ALT indicates significant cytolysis hepatic cells. And mild hyperbilirubinemia was not so high as steadily increased over time. In most patients there is a decrease of the total protein content, namely fraction albumin in serum.

With an increase in viral load in the serum total bilirubin level and the number of platelets is significantly growing ($\rho = 0,6$; $p = 0,04$ and $\rho = 0,6$; $p = 0,004$, respectively). This shows that a high viral load causes these pathological symptoms as hyperbilirubinemia and thrombocytosis (Figure 5).

It is generally known that viral liver disease inhibit hematopoiesis. In patients we studied the presence of a-HDV HDV RNA and the average number of platelets and leukocytes were below - 242.0 vs. 112.0 ($p = 0.02$) and 6.9 versus 4.3 ($p = 0.005$), respectively. In patients with liver cirrhosis observed a similar picture: the mean platelet count was 95.5 versus 168.0 in patients without cirrhosis, leukocytes - 3.4 versus 6.7, respectively ($p = 0.0006$ and $p = 0.0001$). Other parameters were within normal average values.

Ultrasound examination revealed: enlarged liver, diffuse increase in echogenicity, cellular and depleted vascular pattern that shows a picture of chronic hepatitis, as well as the fact that there are changes that are typical lesions of the bile ducts.

Given the common path of infection, a significant proportion of patients detected the mixed infections with hepatitis viruses B, C and D. In our study, triple infection HBV + HDV + HCV was found in three patients, it was 11.5%. HbsAg, a-HDV, a-HCV, the study of PCR detected the hepatitis B virus (DNA of HBV, the viral load of 197,745 copies / ml), - One patient ELISA all serological markers of active replication of hepatitis viruses B, D, and C were identified hepatitis D (HDV RNA) and hepatitis C virus (HCV RNA, genotype 1b). The two other patients in the presence of serum hepatitis virus serological markers of HBV DNA was absent in the presence of HDV RNA and HCV RNA. Thus, in cases of mixed infection HBV + HDV + HCV in the interpretation of serological markers should be borne in mind that between viral agents exist competitive "struggle", and depending on the replicative virus activity may be the prevalence of serological markers of a stronger virus.

All patients with chronic hepatitis D various options for gastritis were found during gastroduodenoscopy. In most cases met superficial gastritis (65.2%). Troubling relatively high frequency of erosive gastritis forms (21.7%), which may be due to microvascular abnormalities in the mucosa of the gastrointestinal tract caused by viral infection.

CONCLUSIONS

Chronic hepatitis D is a major health problem of the Republic of Sakha (Yakutia) as a result of the epidemiological spread, as well as severe and fulminant forms of active viral replication phase period. It found an increase in the intensity of the circulation of HDV-infection among patients with viral hepatitis B.

In the etiological structure of chronic viral hepatitis set the leading role of hepatitis D. Detected high for the Russian Federation the share of chronic hepatitis D in the etiological structure of all of chronic viral hepatitis, amounting to 40.0%. Analysis of the clinical manifestations of data, laboratory and instrumental data of 26 patients with chronic hepatitis D are hospitalized in the department of viral hepatitis YAGKB showed that more than half of the patients were men (54%) and young persons (69%). The most common clinical signs of chronic hepatitis D were liver fibrosis (62.4%), splenomegaly (42.4%) and bloating (41.5%). From the laboratory parameters were below normal average number of platelets above the norm - the median ALT and AST. Viral load averaged ($2648226,0 \pm 953892,7$ Me / ml). Moreover, there is a clear dependence on the degree of increase in transaminases in viral load, the higher the viral load the higher cytolysis of liver cells, confirming the direct effect of cytolytic viruses B and D. In more than half of patients had low activity of HGD, half - a relatively benign course of liver cirrhosis. In a small part of HGD patients noted weakness of the immune response (absence of well-HDV). In 13.6% of cases met mixed infection with hepatitis C. In men, there was a higher activity of HGD and the level of liver enzymes. Most patients with HGD or firmness of temporary disability. High viral load induced hyperbilirubinemia and thrombocytopenia. Liver enzymes are further enhanced with high activity. Thrombocytopenia and leucopenia occurred more frequently in the presence of cirrhosis. Thus, clearly there is a direct relationship between the activity of replicative virus HBV, HDV, and increased activity of aminotransferases. In general, biochemical picture of chronic hepatitis D in HDV replication phase and at a high viral load HBV (up to 10 Mill. Copies / ml) is characterized by cytolytic syndrome, disturbance of protein-synthetic liver function, as reflected

in giperfermentemii and a violation in the coagulation system, followed by a decrease in the number of platelets. In the context of the dynamic observation of this group of patients showed that a high viral load of HBV and HDV replication activity of chronic hepatitis is characterized by progressive course, a bright clinical picture, cytolytic syndrome. Most patients with HGD or firmness of temporary disability. Clinical example proves once again that the simultaneous replication of both viruses HBV and HDV acute hepatitis in a short time becomes chronic with progressive, undulating course with a strong cytolytic syndrome and the formation of liver cirrhosis.

In the region of hepatitis D is registered in 40% of hospitalized patients with viral hepatitis B is more common among most young able-bodied men and occurs mainly in severe and with signs of portal hypertension resulting in fast disability. Thus, the main feature of chronic hepatitis D is its predominant tsirrognost.

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The work was performed as part of the base project № 17.6344.2017

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Received: 18.03.2017

Accepted: 02.07.2017

STEREOMORPHOLOGY OF THE GLANDULAR PARENCHYMA OF THE INFEROPOSTEROLATERAL AREA OF HUMAN PROSTATE GLAND

STEREOMORFOLOGIA MIĄSZU POWIERZCHNI DOLNO-TYLNO-BOCZNEJ LUDZKIEGO GRUCZOŁU KROKOWEGO

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ABSTRACT

Introduction: The human prostate gland contains numerous tubular masses of different calibers in its parenchyma. They form the tubuloalveolar prostate glandules, constituting from numerous prostatic excretory ductules as well as major excretory ducts.

The aim: The study was aimed at 3D visualization of individual microelements of the tubuloalveolar aggregations, localized within the peripheral area.

Materials and methods: To meet the objectives of the study a series of paraffin plane-parallel 4 µm sections has been obtained in the peripheral prostate area. The serial sections were stained with hematoxylin and eosin. After the analysis of the series of sections, the graphical two-dimensional and plastic 3D reconstructions of the investigated microobjects have been made sequentially in depth.

Results: Presence of the epithelial creases and invaginations of the wall in the luminal contour of tubuloalveolar aggregations of the prostate has been found. Creases can be solitary, multiple, or wavy; they can be localized both symmetrically and asymmetrically, with different heights and thicknesses. Intraluminal invaginations, along with the epithelial crease, contain a stromal muscle component with localized blood loop-shaped microvessel. The creases of the glandular epithelium and intraluminal invaginations can "overlap" the lumens of the tubuloalveolar aggregations up to 2/3 of the width, making the inner lumen sinuous that influences the laminar flow of the liquid.

Conclusions: Alternation of the considerable enlargement and narrowing of the inner diameter is common for the tubuloalveolar aggregations which can affect the secreta deposition and movement.

KEY WORDS: human prostate gland, peripheral area, tubuloalveolar aggregations, crease, invagination.

Wiad Lek 2018, 71, 1 cz. II, 184-187

INTRODUCTION

The human prostate gland contains numerous tubular masses of different calibers in its parenchyma. They form the tubuloalveolar prostate glandules, constituting from numerous prostatic excretory ductules as well as major excretory ducts. The term "prostatic ductules" should be interpreted as any ducts of glandular area [1, 2, 3], since no clear landmarks have been found in prostate which would allow distinguishing lobules, sublobular units, acini, adenomeres in its glandular area. Consequently, there are difficulties in attempts to rank the excretory ducts of the prostate. The difficulty of their identification is also in the fact that the glandules of the peripheral area glands are represented by the compound of numerous complex tubuloalveolar microstructures. The acini adhere very close to each other and differ in the variety of shapes of their luminal contours. The excretory microtubes itself are often curved, with heliciform path, complex configuration of the luminal contour, which also makes it difficult for the researcher to be aware of their spatial localization and organization.

THE AIM

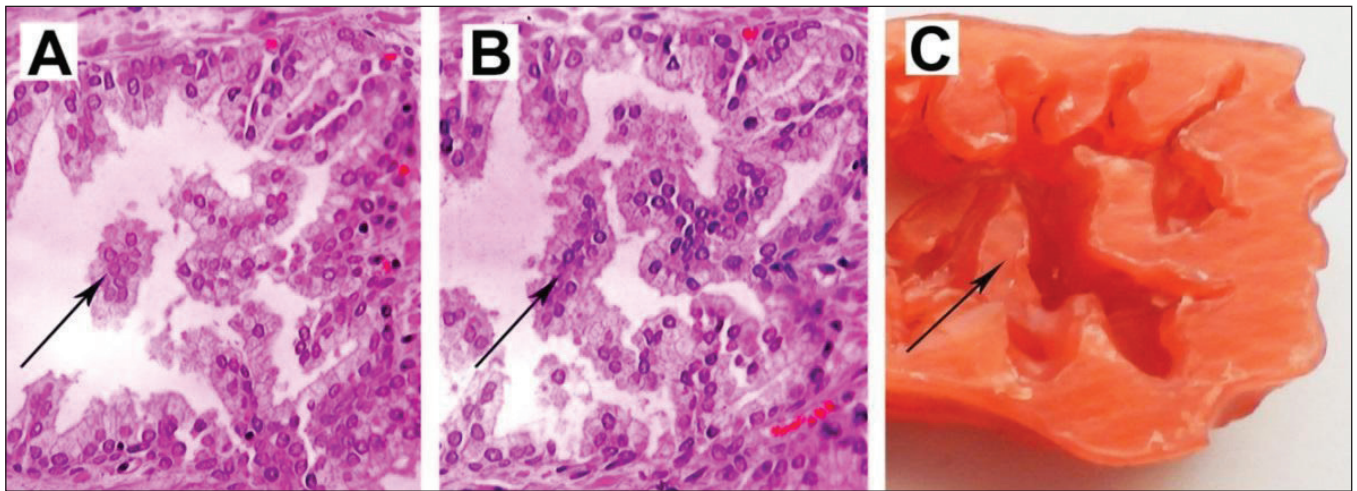
The study was aimed at 3D visualization of individual microelements of the tubuloalveolar aggregations, localized within the peripheral area.

MATERIALS AND METHODS

9 isolated specimens of the prostate taken from men who died of diseases that did not cause changes in the investigated organ. To meet the objectives of the study, we have received a series of paraffin plane-parallel 4 µm sections has been obtained in the peripheral area of the human prostate area. The serial sections were stained with hematoxylin and eosin [4]. After the analysis of the series of sections, the graphical two-dimensional and plastic 3D reconstructions of the investigated microobjects have been made sequentially in depth. The three-dimensional reconstruction of the tubuloalveolar aggregations was performed on their luminal contour [5].

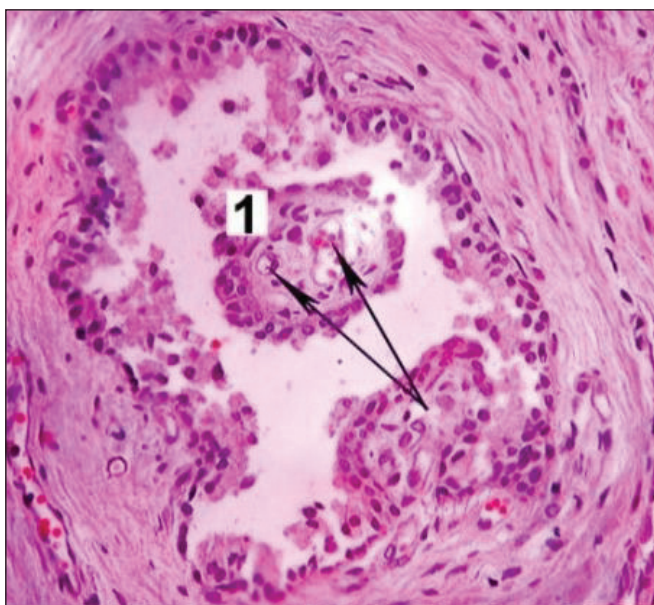
RESULTS

Isolated and "rejected" fragments of tissue can be constantly seen on the histological specimens of the glandular



A – contain the “isolated” fragment; B – the fragment is included into the epithelial crease; C – a fragment of the plastic 3D (“isolated” area of the epithelial lining is marked by the arrow).

Fig. 1. The segment of peripheral area of the human prostate. Hematoxylin and eosin stain. Magnification $\times 400$:



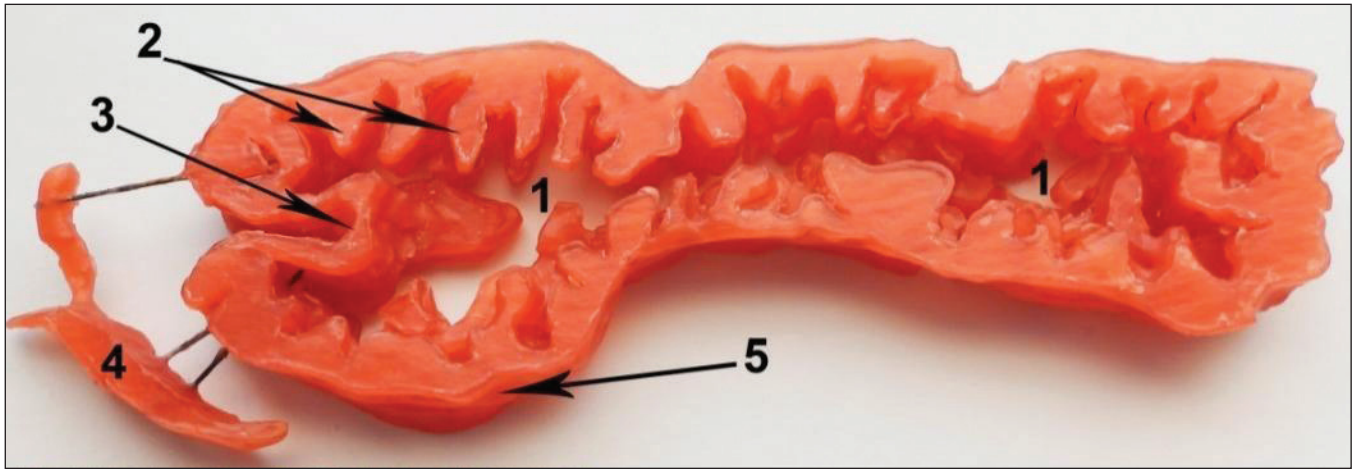
1 – “loose-lying” fragment, containing capillary vessels (marked by arrows).

Fig. 2. The acinus of the peripheral area of the prostate. Hematoxylin and eosin stain. Magnification $\times 400$:

peripheral area of the human prostate in the luminal contour of the tubuloalveolar aggregations. The sequential (line-by-line) analysis of the series of histological specimens and the specimen-based three-dimensional plastic reconstructions allow us to assert that in some cases these are fragments of the glandular epithelium creases of larger or smaller size (Figure 1 A). In other cases such fragments contain, apart from the epithelial lining, the

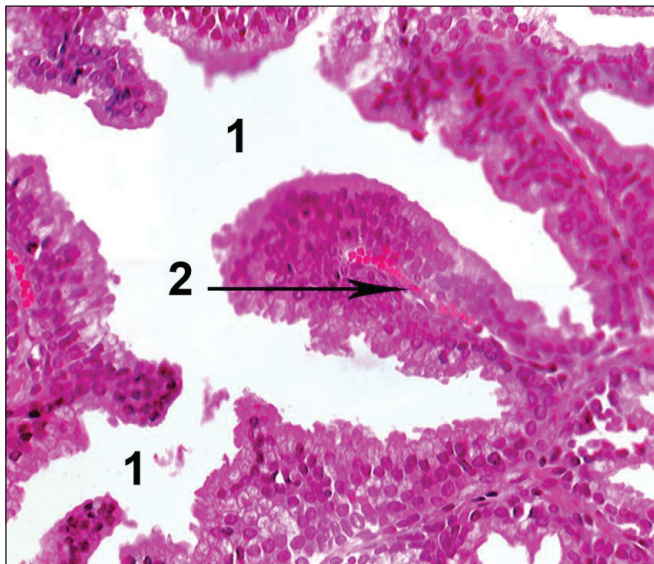
stromal-muscle component and microvessels (Figure 2, 4). Such individual histological section can deceive and lead the researcher to wrong conclusions. Therefore, before any conclusions are to be drawn, it is necessary to try to imagine what is actually above or below the plane of the section. Commonly, our serial specimens and plastic 3D reconstructions clearly show that such loose-lying fragments of tissues are the integral parts of the intraluminal creases of the glandular epithelium or invaginations of all layers of the wall of the tubular structures. Epithelial creases can be solitary or, more commonly, wavy (Figure 1 B). In such cases, the internal surface of the acini and excretory ducts from the side of the luminal contour are pectiniform (Figure 1 C, Figure 3). Intraluminal creases and invaginations of the glandular epithelium can have different parameters and overlap the lumen of the ducts and alveoli up to two thirds of their width. Generally, they almost symmetrically move toward each other from opposite directions, turning the lumen into a fissured spiral space. Three-dimensional plastic reconstructions show that intraluminal invaginations and high epithelial creases are localized in the lumen in different planes, and that’s why they can be seen as isolated from their base on the individual sections. Notably, in normal condition no rugosity of the epithelial lining can occur in the lumen of the tubuloalveolar aggregations on a certain length. In the acini and coherent excretory ductules, abrupt narrowings and ampoule-shaped enlargements of the luminal contour are constantly found. The presence of epithelial creases, invaginations of all elements of the wall, the ampoule-shaped enlargements and its abrupt narrowings contribute to the fact that the luminal contour of the tubuloalveolar aggregations takes the form of the most intricate labyrinth, along which the secreta must move and excrete.

Within the peripheral area, the entire glandular ductal-acinar system, with the exception of the distal seg-



1 – luminal contour; 2 – epithelial creases; 3 – invagination of the wall; 4 – venous microvessels; 5 – outer contour.

Fig. 3. Plastic reconstruction of the excretory ductules of the peripheral area of the prostate. Linear magnification $\times 400$:



1 – lumen of the acinus; 2 – capillary with red blood cells.

Fig. 4. Intraluminal invagination (crest) of the human prostate, containing capillary loop. Hematoxylin and eosin stain. Magnification $\times 400$:

ment of the main excretory ducts near urethra, is layered with the columnar secretory cells which are identical both in the ducts and acini. Notably, this fact is confirmed by the results of the immunohistochemical study of the prostatic specific antigen and the prostatic acid phosphatase. Evidently, there should be no morphological or biological differences between the ductal carcinomas and acinar carcinomas. Apparently, the anomalies of the structural organization of the glands from this area, as well as the other ones, are subjectively defined by the pathologists due to its deviations from the so-called “normal” dimensions and forms of their constituent epithelial secretory components [6].

DISCUSSION

Stereomorphologically, previous study of the microstructure, particularly, the human salivary glands, we have not encountered with any particular difficulty in analyzing, description and spatial reconstruction of their tubular glandular structures, since they are mostly represented by the regular-shaped tubes, gradually changing their outer diameter and the lumen as they approach the common excretory duct. Such system of excretory ducts clearly distinguishes their specific gradations corresponding to the lobe, lobule, sublobule unit and acinus. The outer contour and cavity of their acini were usually regular-shaped and orbicular. At the same time, the acini were quite clearly visualized from the system of the excretory ducts due to the presence of the intercalated segments. These elements could be successfully visualized even when, within the glandular lobule, they had very dense spatial “packing” of their acinar and intercalated segments [7, 8, 9].

On the contrary, the tubuloalveolar components of the human prostate, due to the absence of the intercalated ducts, more resemble “jigsaw puzzles” with the highest degree of adherence to each other, where the connective tissue interlayers are very thin, and, usually, without nonstriated elements. The human prostate is assigned to “compound” glands by some authors, considering the great density of the glandular and non-glandular elements’ composition in different areas [10]. In the luminal contour of the tubuloalveolar aggregations of the prostate gland occurrence of the epithelial creases and invaginations of the wall have been noted, which can “overlap” its lumen up to 2/3 of its width. Creases can be both solitary and multiple, symmetrical, and asymmetric. Invaginations contain stromal muscle component with capillary vessels. The detected alternation of enlargements and narrowings of the luminal contour throughout the tubuloalveolar aggregations is likely to affect the laminar flow of the prostatic secreta.

CONCLUSION

1. In the luminal contour of the ductal-alveolar aggregations the epithelial creases can be solitary, multiple or wavy. They can be localized both symmetrically and asymmetrically and vary in height and thickness.
2. Intraluminal invaginations are also found in the in the luminal contour of the ductal-alveolar aggregations which along with the epithelial crease, contain a stromal muscle component with localized blood loop-shaped microvessel.
3. The creases of the glandular epithelium and intraluminal invaginations can "overlap" the lumens of the tubuloalveolar aggregations up to 2/3 of its width, making the inner lumen sinuous, affecting the laminar flow of the liquid.
4. A regular phenomenon for ductal-alveolar aggregations is the occurrence of the alternating considerable enlargements and narrowings of the inner diameter, which may have some impact on the deposit of the secreta and its movement.

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Received: 01.10.2017**Accepted:** 22.01.2018

CHARACTERIZATION OF LEPR GENE Q223R (RS1137101) GENOTYPES IN PATIENTS WITH KNEE JOINT OSTEOARTHRITIS OF DIFFERENT RADIOGRAPHIC STAGES

CHARAKTERYSTYKA POLIMORFIZMU GENU LEPR Q223R (RS1137101) U PACJENTÓW Z CHOROBA ZWYRODNIENIOWĄ STAWU KOLANOWEGO W RÓŻNYCH STADIACH ZAAWANSOWANIA ZMIAN RADIOLOGICZNYCH

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ABSTRACT

Introduction: Osteoarthritis is a multifactorial joint disease with a significant role of the genetic factor. The numerous studies have demonstrated that genetic dependence is specific for individual hand, hip and knee regions with a genetic contribution to the pathogenesis of osteoarthritis varying from 40% to 65%. To assess the role of leptin gene receptor functional activity disturbance in the pathogenesis of osteoarthritis, it is important to study the relationship between the LEPR gene polymorphism and a number of clinical and laboratory parameters.

The study objective was to determine the relationship between the LEPR gene Q223R (rs1137101) polymorphism and the radiographic stage of osteoarthritis of the knee in female patients of the Ukrainian population.

Materials and methods: The rs1137101 polymorphism was genotyped in 99 female patients diagnosed with osteoarthritis of the knee using polymerase chain reaction in a real-time mode.

Results: It was a tendency of lower prevalence of AA homozygotes and higher prevalence of AG heterozygotes with growing the severity of the disease. The high prevalence of homozygous carriers of the variant allele G in radiographic Stage I patients preconditioned the absence of statistically significant differences in the distribution of genotypes between the groups.

Conclusion: No statistically significant differences in the distribution of prevalence of alleles and LEPR gene Q223R (rs1137101) genotypes in the groups of patients with the knee OA of different radiographic stages have been revealed.

KEY WORDS: knee joint osteoarthritis, LEPR, rs1137101, radiographic stage.

Wiad Lek 2018, 71, 1 cz. II, 188-192

INTRODUCTION

Osteoarthritis (OA) is one of the most common diseases of the joints, the incidence of which increases significantly with age. Chronic progressive OA course leads to deformation of joints, loss of their function and deterioration in the quality of life of patients [1, 2, 3]. There are local and systemic OA risk factors. Among the latter, the most important today are obesity, age, gender, and genetic factors [4]. The numerous studies of family and twins history have demonstrated that genetic dependence is specific for individual areas of hands, hips and knees. The genetic contribution to the pathogenesis of OA varies from 40% to 65%. Most of today's researches suggest that genetic variants of several groups of genes, such as extracellular cartilage matrix structural genes and genes associated with bone metabolism are involved in the OA pathogenesis, including knee joints (*COL2A1*, *COL1A1*, *COL9A1*, *MMPR-1*, *MMP-3*, *MMP-9*, and *VDR1*). Other candidate genes, which may be associated with the risk of knee osteoarthritis, are *GDF5*, *ASP*, *IL-1*, *IL-6*,

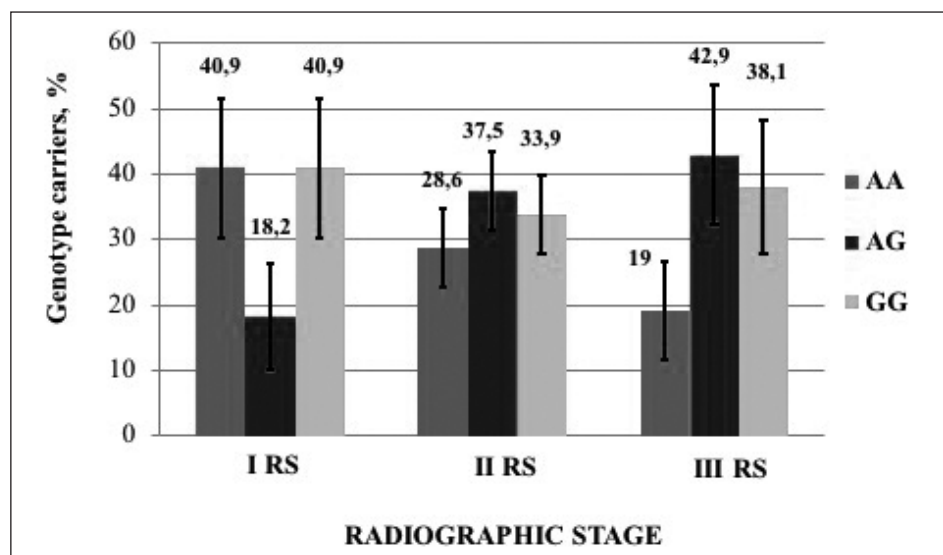
LRCH1, *TNA*, *LRP5*, and *LEP* [5, 6, 7]. It stands to mention that genetic factors involved in the development of OA also have a gender-specific effect, likely influenced by environmental and local biomechanical factors and distributed in different ways between male and female individuals with general prevalence in women rather than in men [7].

A characteristic feature of the OA pathogenesis is abnormal remodeling of articular tissues caused by unbalanced expression of catabolic and anabolic factors by chondrocytes, although all tissues of the joint are involved in the pathogenesis of the disease. Today, one of the most important links in the OA pathophysiology is considered an inflammation process (both local and systemic) controlled by proinflammatory factors produced by cartilage, subchondral bone, and synovial membrane. Subsequently, this pathological process forms a metabolic, and later a functional imbalance of all articular structures with the development of typical clinical picture and uniform pathobiochemical changes [4, 8, 9, 10]. In recent times, researchers have

Table I. Distribution of LEPR gene Q223R (rs1137101) genotypes in groups of patients with different radiographic stages of knee OA.

Genotype	Radiographic stage, n (%)			P*
	I	II	III	
AA	9 (40.91)	16 (28.57)	4 (19.05)	0.36
AG	4 (18.18)	21 (37.5)	9 (42.86)	
GG	9 (40.91)	19 (33.93)	8 (38.09)	

* Fisher`s test 3x3

**Figure 1.** Genotype incidence by polymorphism of LEPR gene Q223R (rs1137101) in groups of patients with different radiographic stages (RS) of knee OA.

become considering an important role of adipose tissue in the development of OA [11, 12, 13, 14]. The relationship between obesity and OA development due to systemic inflammation has become evident. The adipose tissue synthesizes a variety of proinflammatory mediators and adipokines (including leptin) able to affect the components of articular cartilage [4, 15, 16]. The study of leptin role in development of OA has recently been gained a momentum. In addition to the main function of regulating the energy homeostasis, leptin plays a significant role in neuroendocrine interaction, angiogenesis, and bone formation. Leptin exerts its biological activity through connection with OB-Rb, the long isoform of the leptin receptor (encoded by the LEPR gene). Interaction with the LEPR gene product leads to activation of a number of intracellular signaling pathways: JAK-STAT, PI3K, NF- κ B, PKC, MAPK, Erk1/2, and JNK [6]. Taking into account multiple mechanisms of action and diverse ways of regulating metabolic processes involving leptin, some researchers assign it one of the key roles in the OA pathogenesis [4, 16, 17, 18].

Mutations of LEPR gene result in formation of inactive forms of leptin receptors, not capable of providing transduction of the hormonal signal, thus inducing the development of resistance to leptin action. The association of mutations in the leptin gene (LEP) and its receptors (LEPR) with development of obesity, metabolic syndrome, hyperinsulinemia, and other endocrine disorders [19, 20, 21, 22] have been demonstrated. However, the studies of LEPR gene polymorphism connection with OA are quite rare. The association of LEPR gene Q223R (rs1137101)

polymorphism with a risk of development of the knee OA [23, 24] was found in the Chinese and Ukrainian populations, and of hand OA – in Finnish women [25].

To understand the role of disturbance of functional activity of leptin gene receptors in the OA pathogenesis, it is important to study the relationship between the polymorphism of LEPR gene and a number of clinical and laboratory parameters.

THE AIM

The study objective was to investigate a relationship between the LEPR gene Q223R (rs1137101) polymorphism and a radiographic stage of the knee OA.

MATERIALS AND METHODS

We examined 99 women with knee OA, age ($M \pm SD$) 57.60 ± 11.69 , treated at Pyrohov Memorial Vinnytsia Regional Clinical Hospital. The diagnosis was established in accordance with Order of the Ministry of Health of Ukraine No. 676 dated October 12, 2006. Written informed consent was obtained from all subjects before they had started in the study in accordance with the provisions of the Helsinki Declaration; the study protocol had been agreed with the Ethics Commission of Vinnytsia M.I. Pyrohov Memorial National Medical University. The genotyping of LEPR Q223R (rs1137101) polymorphic variants was carried out using the method of real-time allelic-specific polymerase chain reaction (iCycler IQ5, BioRad, USA). The special features of genotype distribu-

Table II. Multiplicative model of LEPR gene rs1137101 inheritance in patients with different radiographic stages of knee OA

Allele (incidence)	II+III RS	I RS	χ^2	P	OR	
	n = 77	n = 22			value	95% CI
A	0.455	0.500	0.28	0.59	0.83	0.43 – 1.63
G	0.545	0.500			1.20	0.61 – 2.35

Table III. Additive model of LEPR gene rs1137101 inheritance in patients with different radiographic stages of knee OA

Genotypes (incidence)	II+III RS	I RS	χ^2	P	OR	
	n = 77	n = 22			value	95% CI
AA	0.260	0.409	0.22	0.64	0.51	0.19 – 1.37
AG	0.390	0.182			2.87	0.89 – 9.31
GG	0.351	0.409			0.78	0.30 – 2.06

Table IV. Dominance model of LEPR gene rs1137101 inheritance in patients with different radiographic stages of knee OA

Genotypes (incidence)	II+III RS	I RS	χ^2	P	OR	
	n = 77	n = 22			value	95% CI
AA	0.260	0.409	1.84	0.17	0.51	0.19 – 1.37
AG + GG	0.740	0.591			1.97	0.73 – 5.31

Table V. Recessive model of LEPR gene rs1137101 inheritance in patients with different radiographic knee OA stages

Genotypes (incidence)	II+III RS	I RS	χ^2	P	OR	
	n = 77	n = 22			value	95% CI
AA + AG	0.649	0.591	0.25	0.62	1.28	0.49 – 3.38
GG	0.351	0.409			0.78	0.30 – 2.06

tion were analyzed in the groups of patients with radiographic Stages I, II and III (no patients with the radiographic Stage IV disease were involved). For the binary analysis, patients with Stage II and III of the disease were combined into a single group to compare with the radiographic Stage I patients.

Differences in the distribution of genotypes in various groups (Tables 2x3 and 3x3) were evaluated using the Fisher's exact test. The method of binary logistic regression was used for evaluation of multiplicative, dominant, recessive (criterion χ^2) and additive (Cochran-Armitage test for trend) inheritance model. The degree of association expressiveness was determined by calculating the odds ratio (OR) and its confidence interval (CI).

RESULTS AND DISCUSSION

We have identified an increased risk of knee OA in the homozygous GG (Arg/Arg) carriers of LEPR gene (rs1137101) compared with the control group of healthy women [23]. The results of analysis of LEPR gene Q223R (rs1137101) genotype distribution in the groups of patients with different radiographic stages of knee OA are shown in Fig. 1

As can be seen in Fig. 1, there are some trends in the distribution of incidence of LEPR gene Q223R (rs1137101) genotypes in the groups of patients with different knee OA stages. In particular, there is a decrease in the proportion of AA (Gln/Gln) genotype carriers at higher stages of the disease - 40.9%, 28.6%,

and 19% at Stages I, II and III, respectively. However, such a decrease did not have a sufficient level of statistical significance ($p = 0.31$, Fisher's exact test). At the same time, the incidence of heterozygous AG (Gln/Arg) carriers grew by 18.2%, 37.5% and 42.9% at Stages I, II and III, respectively, but such growth was not statistically reliable too. One of the reasons for absence of statistically significant differences in the above patterns might be a high incidence of homozygous carriers of the variant allele GG (Arg/Arg) among patients with radiographic Stage I disease - 40.9%, although, when compared with the II and III radiological Stages, this indicator had some gain - 33.9 % and 38.1%, respectively. These were the features that preconditioned the absence of statistically significant differences ($p = 0.36$) in the overall distribution of LEPR gene Q223R (rs1137101) genotypes in patients with different stages of knee OA (Table I).

Given the minimal and moderate difference between II and III radiographic stages, we have also analyzed allelic incidence and genotype distribution patterns in different models of inheritance between groups of patients with I and II + III stages of the disease. The results of the analysis are presented in Tables II - V.

No inheritance model presented with the statistically significant differences. As mentioned above, this was apparently preconditioned by a significant number of genotype GG (Arg/Arg) patients with Stage I OA (40.9%). It's worthy to note that no patients with radiographic Stage IV disease were among patients, therefore it was impossible to analyze the connection of the studied polymorphism with severe knee OA cases.

Comparison of the regularities found in the study with the literature data is considerably complicated by the fact that only few studies of LEPR gene Q223R (rs1137101) polymorphism connection with the risk of development and clinical signs of OA have been conducted so far. In the work by Yang, J. et al., 2016 [24], the association of LEPR gene Q223R (rs1137101) polymorphous variations with the radiographic stage of knee OA in patients belonging to the Northwest Chinese Han population was revealed. According to the authors, the allele G (Arg) carriership had a moderate association with the risk of knee OA in a subgroup with minimal and moderate changes in radiographic indices (II + III Stages), compared with individuals with radiographic stage I (OR = 1.30, 95 % CI: 1.05-1.62; $p = 0.013$) of the disease. Having compared the results obtained in the study with the data provided in the above-mentioned work, it should be noted that, firstly, the lack of statistically significant differences in our work may be, to some extent, preconditioned by a significantly smaller number of study subjects (99 individuals), compared with the one from the work by Yang, J. et al., (2016), which involved 1215 subjects with similar indices obtained: OR = 1.20 (allele G (Arg) carriership, see Table II). Although the main factor, most likely, should have been considered the high incidence of homozygous GG (Arg/Arg) carriers in radiographic Stage I patients. Therefore, it's worthy to note that the above-mentioned work [24] did not presented with a connection between distribution of genotypes and allele incidence when comparing the results from the control group (Radiographic stage I) with the data of a subgroup of patients with severe changes (radiographic stage IV) [24]. Given the absence of radiograph stage IV patients among the patients examined by us, it is not possible to compare the patterns revealed in this work. We assume that the course of disturbances associated with LEPR gene Q223R (rs1137101) polymorphism has a chronic, prolonged nature; therefore, the complications in homozygous carriers related to radiographic indicators are manifested in more distant periods of the disease.

S. Hämäläinen et al., 2017 found a weak association of AC LEPR (rs1137101, rs1805094) (OR = 1.54, 95% CI: 1.01-2.35, $p = 0.05$) haplotype with radiographic indices in women of Finnish population with OA of hand joints. However, it should be noted that the criteria used by the authors for distribution of patient into subgroups differed from those used in our study [26].

CONSLUIONS

We did not find any statistically significant differences in the distribution of alleles and LEPR gene Q223R (rs1137101) genotype in knee OA patients at different radiographic stages. We consider promising further research of the relationship between the LEPR gene Q223R (rs1137101) polymorphism and such clinical and laboratory parameters of knee OA patients as a body mass index and leptin concentration.

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State registration number 0107U003479. It is a fragment of a research work “Clinical-laboratory and psychological predictors of severity of the clinical course and functional failure in patients with systemic connective tissue diseases and fibromyalgia”

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Received: 20.11.2017

Accepted: 05.02.2018

EPIDEMIOLOGIA NAGŁEGO ZATRZYMANIA KRĄŻENIA W OPIECE PRZEDSZPITALNEJ NA TERENIE WOJEWÓDZTWA ŚLĄSKIEGO

THE EPIDEMIOLOGY OF SUDDEN CARDIAC ARREST IN PREHOSPITAL CARE IN THE AREA OF THE SILESIA VOIVODESHIP

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STRESZCZENIE

Wstęp: Nagłe zatrzymanie krążenia (NZK) jest poważnym problemem medycznym i społecznym. Występowanie NZK jest zróżnicowane pod względem miejsca, czasu oraz okoliczności.

Cel pracy: Analiza retrospektywna przypadków pozaszpitalnego NZK w populacji objętej działalnością Wojewódzkiego Pogotowia Ratunkowego (WPR) w Katowicach pod względem epidemiologicznym.

Materiał i metody: Analizie poddano karty zlecenia wyjazdu oraz karty medycznych czynności ratunkowych WPR w Katowicach za rok 2016 (N = 249 872). Do badania retrospektywnego włączono przypadki, które kończyły się przypadkiem pozaszpitalnego NZK u osób dorosłych (N = 1603). Parametry ilościowe przedstawiono jako wartości średnie wraz z odchyleniem standardowym. Zmienne niemetryczne opisano za pomocą wskaźników struktury. Analizę porównawczą przeprowadzono z wykorzystaniem testu t-studenta dla zmiennych ilościowych oraz testu χ^2 Pearsona dla zmiennych niemetrycznych. Dla wszystkich analiz istotność statystyczną przyjęto na poziomie 0.05.

Wyniki: W badanej grupie było 1005 mężczyzn (62,7%), 566 kobiet (35,3%) oraz 32 przypadki (2,0%), dla których brak określenia płci. Kobiety zasadniczo były starsze niż mężczyźni (p = 0,000). Średnia wieku w grupie pacjentów wyniosła 65,7 roku. Współczynnik zapadalności w NZK wyniósł 59,37/100 000. Najczęściej do wystąpienia NZK dochodziło w warunkach domowych (71,1%, p = 0,000). Najczęściej w obecności świadka zdarzenia (około 70,0% przypadków, p = 0,000). Najwięcej epizodów NZK odnotowano w pierwszym kwartale roku, a najmniej w trzecim (28,4% vs. 22,5%). Najczęściej do NZK dochodziło w ciągu dnia. Powrót spontanicznego krążenia zanotowano w 33,4% przypadków.

Wnioski: Częstość występowania NZK jest sporadyczna w stosunku do wszystkich realizowanych wizyt w badanym okresie, lecz epizody te obarczone są dużym niepowodzeniem. Prowadzenie działań zgodnie z aktualną wiedzą prawdopodobnie spowoduje dużo wyższy wskaźnik ROSC.

SŁOWA KLUCZOWE: nagła śmierć sercowa, zespół ratownictwa medycznego, resuscytacja

ABSTRACT

Introduction: Sudden cardiac arrest (SCA) is a serious medical and social issue. The incidence of SCA varies depending on the location and the circumstances.

The aim: A retrospective analysis of non-hospital SCA cases from an epidemiological perspective. The research involved the population monitored by the Voivodeship Rescue Service (VRS) in Katowice.

Material and methods The analysis covered dispatch order forms and emergency medical procedure forms of the VRS in Katowice in 2016 (n = 249 872). The retrospective analysis involved cases of non-hospital SCA in adults (n = 1603). Quantitative parameters have been presented as average values with standard deviation. Non-metric variables have been described by means of structure indicators. A comparative analysis was conducted by means of the Student's T-test for the quantitative variables and the Pearson's chi-squared test for the non-metric variables. The statistical significance adopted for the purpose of all analyses was 0.05.

Results: There were 1005 men (62.7%), 566 women (35.3%) and 32 cases (2.0%) where gender identification was not reported. Female individuals were generally older than male individuals (p = 0.000). Patients' average age was 65.7 years. The SCA attack rate was 59.37/100 000. SCA cases were usually reported in domestic conditions (71.1%, p = 0.000). In a majority of cases, the incident was witnessed by a third person (about 70.0% of cases, p = 0.000). Most of the SCA cases were reported in the first quarter of the year whereas the lowest number of cases was noticed in the third quarter (28.4% vs 22.5%). SCA was most frequent during the day. Restoration of spontaneous circulation was reported in 33.4% of the cases.

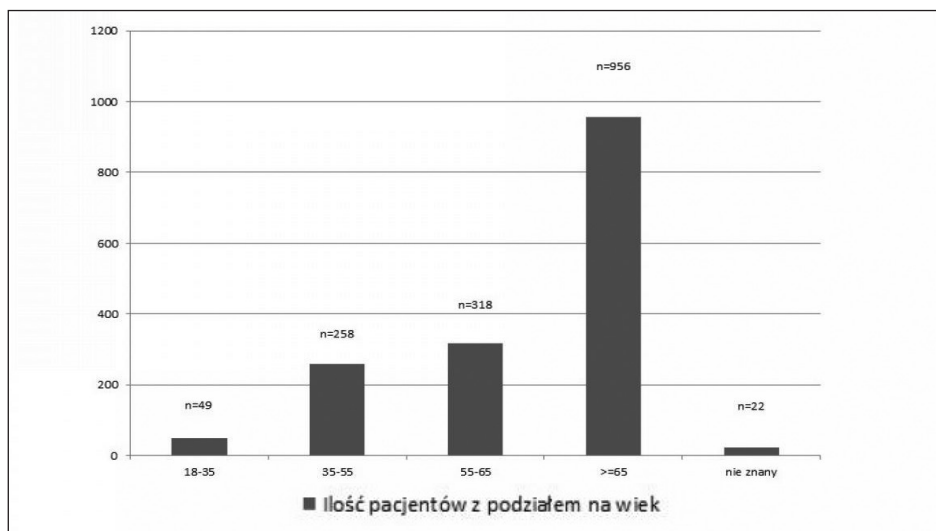
Conclusions: The incidence of SCA is occasional in the context of all analyzed emergency cases in the period under research. However, SCA cases are related with a high risk of failure. Acting according to the currently available knowledge will probably cause an increase of the restoration of spontaneous circulation (ROSC) rate.

KEY WORDS: sudden cardiac death (SCD), emergency medical team, resuscitation

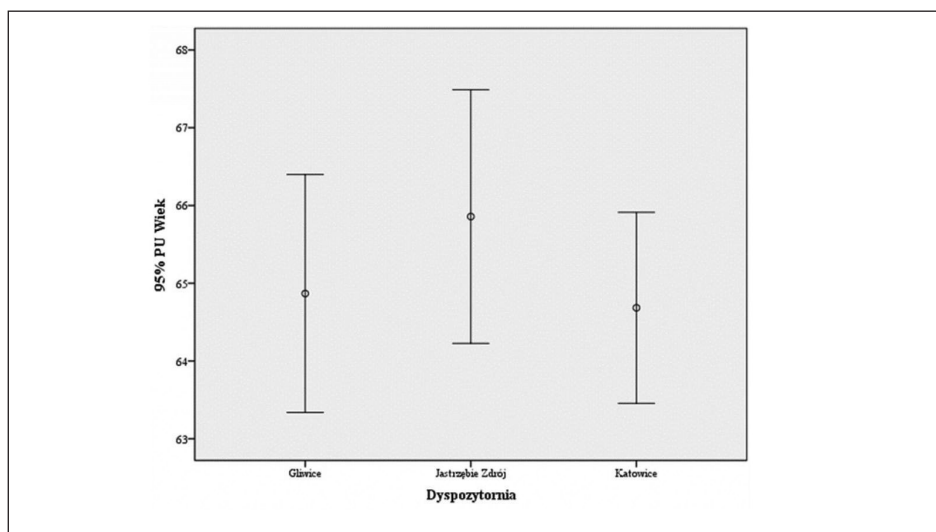
WSTĘP

Nagle zatrzymanie krążenia (NZK) jest poważnym zdarzeniem medycznym, które może wystąpić w najmniej oczekiwanym miejscu i czasie. Jest bardzo poważnym problemem medycz-

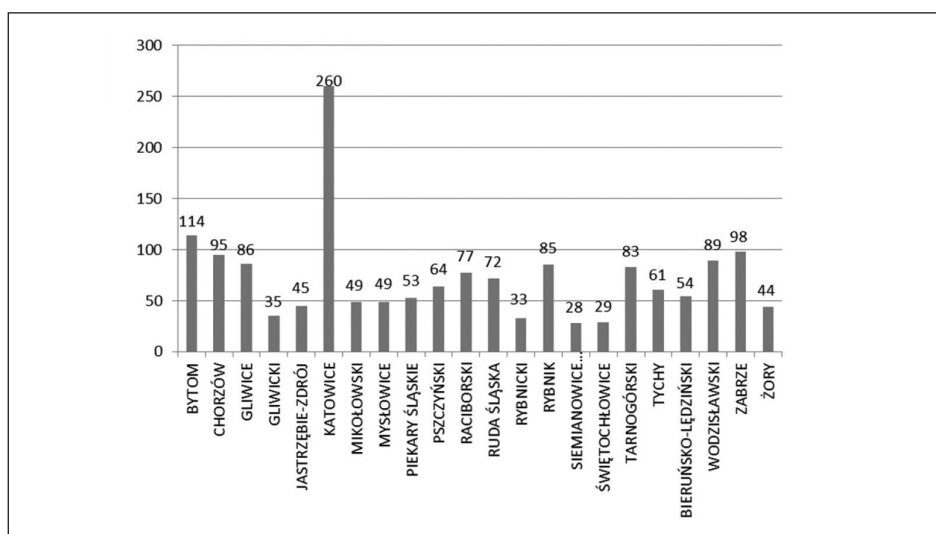
nym i społecznym [1]. NZK może być spowodowane różnymi czynnikami, zarówno chorobowymi, jak i urazowymi. Wymaga bezwzględnego podjęcia czynności ratunkowych zarówno przez świadków zdarzenia, jak i wykwalifikowane zespoły



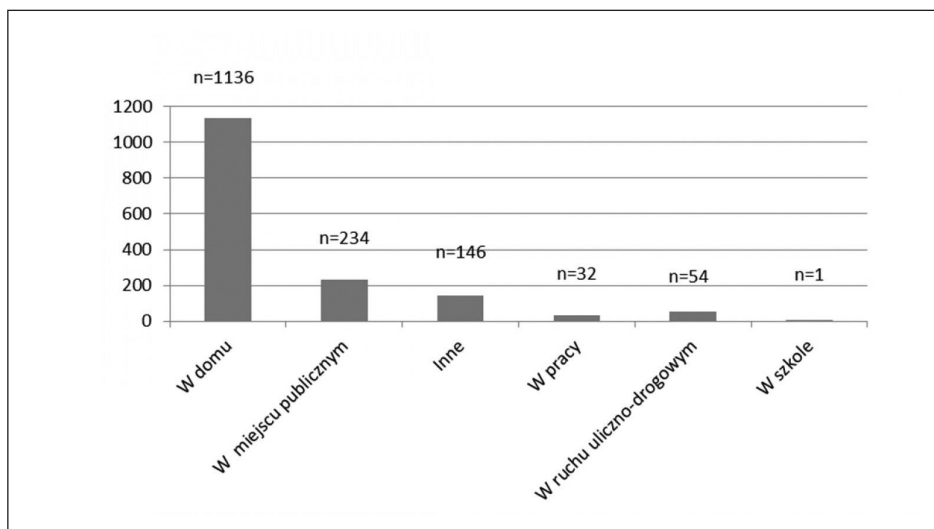
Ryc. 1. Podział pacjentów z pozaszpitalnym NZK z podziałem na grupy wiekowe.



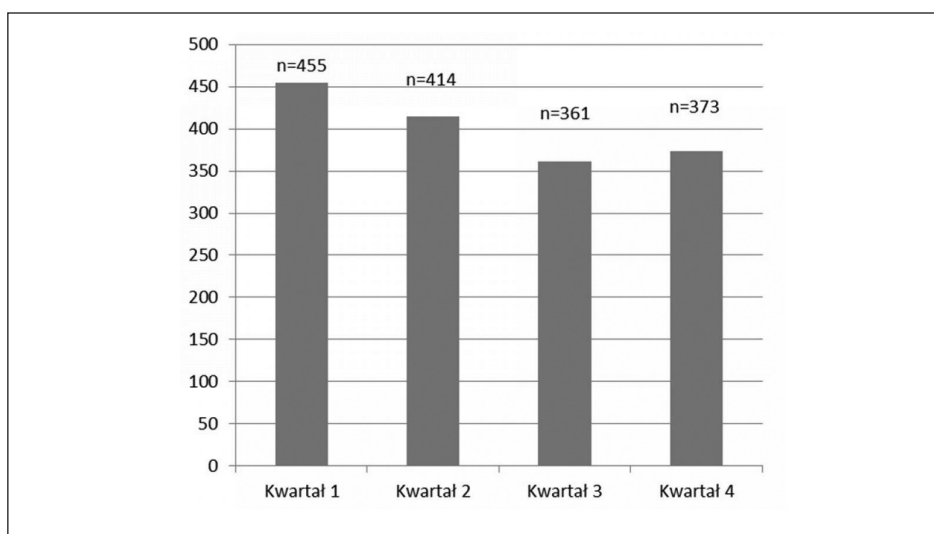
Ryc. 2. Średnia wieku pacjentów z pozaszpitalnym nagłym zatrzymaniem krążenia z podziałem na dyspozytornie medyczne.



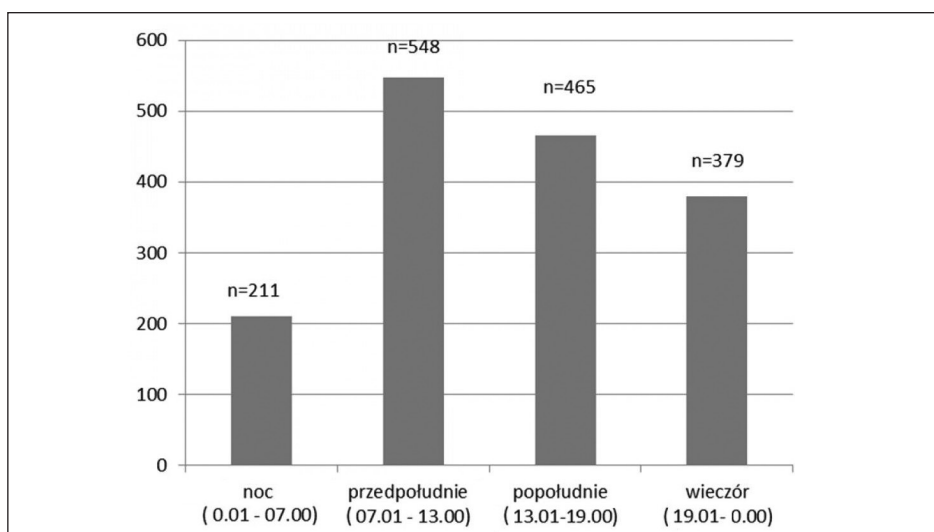
Ryc. 3. Podział wizyt zespołów ratownictwa medycznego ze względu na miasta na prawach powiatu oraz powiaty.



Ryc. 4. Podział wizyt do pozaszpitalnego NZK zespołów ratownictwa medycznego ze względu na lokalizację zdarzenia.



Ryc. 5. Liczba zgłoszeń do pozaszpitalnego nagłego zatrzymania krążenia w kolejnych kwartałach roku.



Ryc. 6. Struktura pozaszpitalnego NZK w poszczególnych porach dnia.

ratownictwa medycznego. NZK w Europie rozpoznaje się u 38/100 000 mieszkańców w skali roku [2, 3], natomiast w Stanach Zjednoczonych u 76/100 000 mieszkańców rocznie [4]. Na świecie istnieje wiele rejestrów pozaszpitalnego NZK [5,6].

W ostatnich latach rejestry NZK wskazują na wzrost odsetka powrotów spontanicznego krążenia w Europie i na świecie, lecz przeżywalność pacjentów do wypisu ze szpitala dalej jest bardzo niska i wynosi tylko 10,6% [7].

Tabela I. Liczba mieszkańców miast na prawach powiatu działalnością objętą przez WPR w Katowicach.

Miasto na prawach powiatu	Liczba ludności w tys. (stan na 30.06.2016)	Liczba realizowanych wizyt w 2016 roku	Liczba realizowanych wizyt do pozaszpitalnego NZK w 2016 roku	Procent wizyt wizyt do pozaszpitalnego NZK w stosunku do wszystkich realizowanych wizyt w 2016 roku
Chorzów	115,538	13435	95	0,70
Gliwice	187,993	19567	86	0,43
Jastrzębie Zdrój	94,073	9120	45	0,49
Katowice	303,314	42346	260	0,61
Mysłowice	76,028	7100	49	0,69
Piekary Śląskie	58,978	4560	53	1,16
Rybnik	149,094	12340	85	0,68
Siemianowice Śląskie	69,658	7148	28	0,39
Ruda Śląska	148,090	15469	72	0,46
Świętochłowice	51,722	4561	29	0,63
Tychy	135,698	12348	61	0,49
Zabrze	184,815	17450	98	0,56
Żory	63,015	5487	44	0,80
Bytom	179,762	18456	114	0,61
ŁĄCZNIE	1,817,778	189387	1119	

Tabela II. Liczba mieszkańców powiatów działalnością objętą przez WPR w Katowicach.

Powiaty	Liczba ludności w tys. (stan na 30.06.2016)	Liczba realizowanych wizyt w 2016 roku	Liczba realizowanych wizyt do pozaszpitalnego NZK w 2016 roku	Liczba procentowa wizyt do pozaszpitalnego NZK w stosunku do wszystkich realizowanych wizyt w 2016 roku
bieruńsko-lędzki	58,723	4354	54	1,24 %
gliwicki	116,349	7960	35	0,43 %
mikołowski	98,039	8609	49	0,56 %
pszczyński	110,065	6450	64	0,99 %
raciborski	109,478	7340	77	1,04 %
wodzisławski	157,835	10364	89	0,85 %
rybnicki	79,024	5084	33	0,64 %
tarnogórski	143,386	10234	83	0,81 %
SUMA	872,899	60395	484	

Dużą rolę w skuteczności działania odgrywa świadek zdarzenia, jeśli szybko zareaguje i rozpocznie resuscytację zwiększa szanse pacjenta na powrót krążenia. Tylko około 20–25% przypadków pierwszym zdiagnozowanym rytmem przez zespół ratownictwa medycznego to migotanie komór [8]. Jeśli natomiast świadek zdarzenia wykorzysta automatyczny defibrylator zewnętrzny (AED), to odsetek ten wyniesie od 59% do nawet 76% [9, 10].

CEL PRACY

Celem pracy była analiza retrospektywna przypadków NZK w opiece przedszpitalnej w populacji objętej działalnością Wojewódzkiego Pogotowia Ratunkowego (WPR) w Katowicach pod względem epidemiologicznym.

MATERIAŁ I METODY

Analizie poddano karty zlecenia wyjazdu oraz karty medycznych czynności ratunkowych WPR w Katowicach za rok 2016 (N = 249 872). Do badania retrospektywnego włączono jedynie przypadki, które kończyły się epizodem pozaszpitalnego NZK (zgodnie z międzynarodową statystyczną kwalifikacją chorób i problemów zdrowotnych ICD-10 – rozpoznanie I46 – nagłe zatrzymanie krążenia), wyłączając pacjentów poniżej 18. roku życia. Powyższe kryteria włączenia spełniło 1603 przypadki, co stanowiło 0,64% wszystkich zdarzeń z analizowanego okresu.

WPR w Katowicach to największy publiczny dysponent w Polsce, który na co dzień zabezpiecza populację około 2,7 mln mieszkańców województwa śląskiego. Zespoły zarządzane są przez 3

Tabela III. Liczba przypadków pozaszpitalnego nagłego zatrzymania krążenia w poszczególnych miesiącach roku wraz z podziałem na dyspozytornie medyczne.

Miesiąc	Dyspozytornia Jastrzębie Zdrój	Dyspozytornia Gliwice	Dyspozytornia Katowice
Styczeń	28	52	70
Luty	30	36	69
Marzec	51	49	70
Kwiecień	29	46	55
Maj	38	40	63
Czerwiec	31	42	70
Lipiec	27	37	57
Sierpień	34	41	61
Wrzesień	30	23	51
Październik	28	34	55
Listopad	25	30	60
Grudzień	33	37	71
SUMA	384	467	752

Tabela IV. Analiza procentowa przypadków NZK w poszczególnych miesiącach.

Miesiąc	SUMA zdarzeń z pozaszpitalnym NZK	Odsetek wszystkich zdarzeń z NZK w danym miesiącu roku [%]
Styczeń	150	9,35
Luty	135	8,42
Marzec	170	10,60
Kwiecień	130	8,10
Maj	141	8,79
Czerwiec	143	8,92
Lipiec	121	7,54
Sierpień	136	8,48
Wrzesień	104	6,48
Październik	117	7,29
Listopad	115	7,17
Grudzień	141	8,79
ŁĄCZNIE	1603	

zintegrowane dyspozytornie medyczne (trzy rejony operacyjne), które znajdują się w Katowicach (41 zespołów), Gliwicach (25 zespołów) i Jastrzębiu Zdrój (19 zespołów). W zintegrowanej dyspozytorni medycznej pracują dyspozytorzy medyczni, którzy przyjmują wezwania z numeru alarmowego 999 oraz przekierowane z numeru 112 od operatora z Urzędu Wojewódzkiego. W 2016 roku WPR w Katowicach odebrał prawie 620 tysięcy telefonów i zrealizował prawie 250 tysięcy wizyt. Województwo śląskie jest podzielone na 19 miast na prawach powiatów oraz 17 powiatów. Na III stopniu podziału administracyjnego, województwo składa się ze 167 gmin, w tym 49 gmin miejskich, 22 gmin miejsko-wiejskich oraz 96 gmin wiejskich. Działalność WPR w Katowicach obejmuje z tego 14 miast na prawach powiatu oraz 8 powiatów. Największym miastem na prawach powiatu są Katowice (303 tys. mieszkańców), najmniejszym Świętochło-

wice (51 tys. mieszkańców). Natomiast największym powiatem jest powiat wodzisławski (157 tys. mieszkańców) a najmniejszy powiat bieruńsko-lędziński (58 tys. mieszkańców).

Szczegółowej analizie poddano dane demograficzne zdarzeń, w których wystąpiło pozaszpitalne NZK tj. płeć, wiek, miejsce, czas (kwartał, miesiąc i pora dnia) oraz rodzaj zdarzenia wraz z podziałem ze względu na powiaty. Dodatkowo oszacowano współczynnik zapadalności i wskaźnik śmiertelności z powodu nagłego zatrzymania krążenia.

Zmienne ilościowe o rozkładzie normalnym przedstawiono za pomocą parametrów statystyki opisowej: średnia wraz z odchyleniem standardowym. Zmienne niemetryczne przedstawiono z wykorzystaniem wskaźników struktury: liczebność oraz odsetki. Analizę porównawczą w przypadku zmiennych ilościowych przeprowadzono z wykorzystaniem

testu t-studenta lub U Manna-Whitney'a w zależności od postaci rozkładu. Dla zmiennych niemetrycznych w analizie porównawczej posłużono się testem χ^2 Pearsona. Dla wszystkich analiz wartość istotności statystycznej przyjęto na poziomie 0,05. Obliczenia wykonano przy użyciu programu STATISTICA wersja 6.1 (Statsoft Inc.) oraz IBM SPSS 24.0.

Chociaż najważniejszym czynnikiem skuteczności działań w ramach systemu ratownictwa medycznego przedszpitalnego nie jest powrót spontanicznego krążenia, lecz przeżywalność pacjenta do wypisu ze szpitala. Zakres naszego badania nie obejmował tego elementu.

WYNIKI

W 2016 roku na terenie działalności WPR w Katowicach odnotowano 1603 przypadki pozaszpitalnego NZK u osób dorosłych, a powrót spontanicznego krążenia wyniósł 33,4% (N = 546). W całej grupie badanej było 1005 mężczyzn (62,7%), 566 kobiet (35,3%) oraz 32 przypadki (2,0%) dla których brak było danych określających płeć. Kobiety zasadniczo były starsze niż mężczyźni ($p = 0,000$). Analiza krzyżowa pomiędzy płcią a poszczególną dyspozytornią medyczną nie wykazała istotności statystycznej ($p = 0,3888$).

Średnia wieku w grupie pacjentów z pozaszpitalnym NZK wyniosła 65,7 roku. Została również wykonana analiza wieku badanych z podziałem na grupy wiekowe (Ryc. 1). W przedziale od 18. do 35. roku życia zanotowano tylko 49 przypadków (3,0%), ale już w przedziale powyżej 65 roku życia 956 przypadków (59,6%). Dokonano również analizy wieku z podziałem na poszczególne dyspozytornie medyczne (Ryc. 2). Współczynnik zapadalności w pozaszpitalnym NZK wyniósł w badanej populacji 59,37/100000 ludności i był prawie dwukrotnie wyższy u mężczyzn (37,22/100000) niż u kobiet (20,96/100000). Zapadalność rosła wraz z wiekiem badanych.

Najwięcej zdarzeń, w których wystąpiło pozaszpitalne NZK, to największe powiaty objęte działalnością WPR w Katowicach. Najwięcej odnotowano w powiecie katowickim 260 przypadków NZK (16,2%) a najmniej w powiecie siemianowickim 28 przypadków (1,7%) (Ryc. 3). W powiecie katowickim również zarejestrowano najwięcej realizowanych wizyt 42 346 (17,0%), a najmniej w powiecie bieruńsko-lędzińskim 4354 (1,7%) (Tab. I). Najczęściej procentowo pozaszpitalne NZK w stosunku do wszystkich realizowanych wizyt w danych powiecie w 2016 roku miało miejsce w powiecie bieruńsko-lędzińskim (1,2%) a najrzadziej w powiecie Siemianowice Śląskie (0,39%) (Tab. II). Średnia występowania pozaszpitalnego NZK w stosunku do wszystkich realizowanych wizyt wyniosła 0,64 %.

Najczęściej do wystąpienia pozaszpitalnego NZK dochodziło w warunkach domowych (N=1136, 71,1%, $p = 0,000$), następnie w miejscu publicznym (N=234, 14,5%) najmniej w szkole (N = 1, 0,06%) (Rycina 4). Poza domem częściej do NZK dochodziło u mężczyzn niż w domu ($p < 0,015$). Najczęściej w obecności świadka zdarzenia (około 70% przypadków, $p = 0,000$).

Zauważono znaczne różnice pomiędzy poszczególnymi kwartałami roku. W pierwszym kwartale przypadków po-

zszpitalnego NZK było 455 co stanowiło 28,4% wszystkich przypadków, ale już w trzecim kwartale odnotowano 361 przypadków, co stanowiło 22,5% (Ryc. 5). Należy zauważyć, że w poszczególnych kwartałach łączna liczba wszystkich realizowanych wizyt była zbliżona.

Stwierdzono istotne różnice pomiędzy poszczególnymi miesiącami, w których wystąpiło pozaszpitalne nagłe zatrzymanie krążenia. Najczęściej do pozaszpitalnego NZK dochodziło na zintegrowanej dyspozytorni medycznej w Katowicach (N = 752) a najmniej w dyspozytorni medycznej w Jastrzębiu Zdrój (N = 384) (Tabela III). Najwięcej zdarzeń miało miejsce w marcu (N = 170, 10,6%), a najmniej we wrześniu (N = 104, 6,5%) (Tab. IV).

Najczęściej do pozaszpitalnego NZK dochodziło w ciągu dnia (od godziny 07.01 do godziny 19.00) (63,2%), znacznie rzadziej wieczorem i w ciągu nocy (od godziny 19.01 do godziny 07.00) (36,8%) (Ryc. 6).

DYSKUSJA

Celem pracy było przedstawienie danych epidemiologicznych związanych z przypadkami przedszpitalnego NZK w populacji objętej działalnością WPR w Katowicach podczas 12-miesięcznej obserwacji. Odsetek zachorowalności badanej populacji wyniósł 59,37/100 000 mieszkańców. Porównując te dane z dostępnym piśmiennictwem możemy zauważyć dużą rozbieżność. W pracy Gacha D i wsp [11] odsetek ten jest na poziomie 170/100 000 (dane z 2013 r.), więc prawie trzykrotnie wyższy, a dotyczy tego samego województwa (śląskiego). W innych krajach Europy Zachodniej współczynnik ten jest bardzo podobny do naszych danych, na przykład w Danii 34/ 100 000 [12], w Szwecji 52/100 000 [13], ale już w Austrii jest nawet wyższy niż w pracy Gacha D i wsp 206/100 000 [14]. Różnice te mogą wynikać z charakterystyki populacji lub być uwarunkowane różnymi systemami raportowania i gromadzenia danych medycznych. Warto zaznaczyć, że Polska nie prowadzi żadnego ogólnopolskiego rejestru NZK zarówno w opiece przedszpitalnej, jak i wewnątrzszpitalnej. Nawet w programie EuReCa ONE tylko 6% powierzchni kraju było objęte badaniem.

Przedszpitalne NZK prawie dwukrotnie częściej dotyczyło mężczyzn niż kobiet. Podobny współczynnik można zauważyć w innych publikacjach [15, 16]. Mediana wieku badanych wyniosła 65,7 roku, kobiety zasadniczo są starsze niż mężczyźni. Wiąże się to również z średnią długością życia (kobiety żyją dłużej o około 8 lat niż mężczyźni). Pomimo tak wielu różnic, przeżycie w szpitalu i wynik neurologiczny są zazwyczaj podobne [17].

Województwo Śląskie, a dokładniej aglomeracja Katowicka (kilkanaście miast skupionych w jednym miejscu), jest bardzo specyficznym regionem. Jest tu więcej miast na prawach powiatu niż samych powiatów. Choć wyniki bardzo różnią się. Dla przykładu w powiecie bieruńsko-lędzińskim trzykrotnie więcej odnotowano epizodów NZK niż w powiecie Siemianowice Śląskie (1,24% vs. 0,39%), trudno racjonalnie wytłumaczyć ten fakt.

Najczęstszym miejscem wystąpienia NZK był dom osoby poszkodowanej. Jednak NZK dotyczy osób starszych,

często już z obciążającym wywiadem medycznym. Najczęściej do NZK dochodzi w obecności świadka zdarzenia, choć w innych publikacjach odsetek ten jest dużo wyższy niż w badaniu własnym [18, 19]. Niewątpliwie obecność świadka na miejscu zdarzenia powoduje dużo szybsze uruchomienie całego systemu ratownictwa medycznego i znacząco skraca czas rozpoczęcia uciskania klatki piersiowej, jako najważniejszego elementu działań ratowniczych.

Najczęściej do NZK dochodziło w pierwszym kwartale roku (28,5%), co można tłumaczyć tym, że w pierwszych trzech miesiącach roku, również jest największy odsetek realizowanych wizyt, co może korelować z epizodami NZK. Podobnie jest w przypadku pory dnia, najczęściej dotyczy to godzin pomiędzy 07.00 a 19.00. W doniesieniach naukowych występowanie pozaszpitalnego NZK może się różnić w zależności od pory dnia czy miesiąca roku [20]. Różnice mogą wynikać z miejsca zamieszkania lub warunków pogodowych [21]. Zmiany sezonowe mogą z kolei zależeć od względnych zmian klimatu i pogody [22].

Niezależnie od okoliczności zatrzymania krążenia, im więcej czasu upływa od utraty przytomności do podjęcia resuscytacji krążeniowo-oddechowej, tym niższe są szanse pacjenta na przeżycie. W całej badanej grupie powrót spontanicznego krążenia wyniósł 33,4% (N = 546), w Europie poziom ten wynosi średnio 38,0% [23]. Wynik ten, jest więc zbliżony do danych podawanych przez inne źródła [24,25].

WNIOSKI

Częstość występowania pozaszpitalnego NZK jest sporadyczna do wszystkich realizowanych wizyt w badanym okresie, lecz obciążona jest dużą śmiertelnością. Częściej pozaszpitalne NZK występuje u mężczyzn niż u kobiet, lecz kobiety zasadniczo są starsze. Średnia wieku badanych wyniosła 65,7 lat. Współczynnik zapadalności wyniósł 59,37/100 000. Najczęściej do NZK dochodziło w domu w obecności świadka zdarzenia. Do NZK najczęściej dochodzi w ciągu dnia i w pierwszym kwartale roku. Powrót spontanicznego krążenia zanotowano w 33,4% przypadków. Ważnym aspektem skuteczności działań jest prowadzenie resuscytacji zgodnie z aktualną wiedzą medyczną. Lekarze, ratownicy medyczni, pielęgniarki powinni być szkoleni przynajmniej raz do roku z zaawansowanych procedur resuscytacyjnych. Cykliczne szkolenia pozwolą na utrzymanie na najwyższym poziomie wiedzy i umiejętności członków zespołu ratownictwa medycznego.

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Nadesłano: 05.01.2018

Zaakceptowano: 05.02.2018

INTERNATIONAL MEDICAL LAW AND ITS IMPACT ON THE UKRAINIAN HEALTH CARE LEGISLATION

MIĘDZYNARODOWE PRAWO MEDYCZNE I JEGO WPŁYW NA AKTY PRAWNE DOTYCZĄCE OCHRONY ZDROWIA NA UKRAINIE

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ABSTRACT

Introduction: The Ukrainian state has an urgent necessity of rapid search for essentially new legal and organizational forms of the healthcare system, reform of the legal regulation of healthcare services provision. In the context of European integration, the advancement of the medical industry reform is closely related to consideration of international standards and norms of health care.

The aim: To study the impact of international medical law on the Ukrainian health care legislation.

Materials and methods: International and Ukrainian regulations and documents on health care were used in the research. System and structural, functional and legal comparative methods as well as systematization, analysis and synthesis were determinative in the research process.

Review: Systematization of international documents on health care was made. The major problems in the Ukrainian health care legislation were determined in terms of their conformity with the international legislative norms. The expediency of the Medical Code adoption was grounded and its structure was defined.

Conclusions: Most health care international acts are ratified by Ukraine and their provisions are implemented in the legislation. Simultaneously, there is a row of problems, which hinder the Ukrainian health care development and place obstacles in the way of European integration. To remove these obstacles, it is expedient to create a codified act – the Medical Code, which would systematize the provisions of the current medical laws and regulations and fill in the existing gaps in the legal regulation of health care.

KEY WORDS: medical law, international medical law, international document, health care, codification of medical law.

Wiad Lek 2018, 71, 1 cz. II, 201-205

INTRODUCTION

The Ukrainian state has an urgent necessity of rapid search for essentially new legal and organizational forms of the healthcare system, reform of the legal regulation of healthcare services provision. In the context of European integration the advancement of the medical industry reform is closely related to consideration of international standards and norms of health care. Not only new realities bring difficulties but also open up new possibilities in this field. In the final analysis, exercise of the citizens' constitutional right to health care depends on the content and orientation of the medical industry reform. International medical law is of great significance for modernization of the healthcare system and medical law in Ukraine.

THE AIM

The aim of the given article is to study the impact of international medical law on the Ukrainian health care legislation.

MATERIALS AND METHODS

The analysis of scientific sources shows that the subject matter of medical law and separate matters of international

medical law were studied by the following scientists, namely Z. Hladun, I. Zohyi, O. Klymenko, V. Pashkov, I. Seniuta, R. Stefanchuk, S. Stetsenko, V. Stetsenko and others. Meanwhile, the issue of international medical law impact on the Ukrainian health care legislation has not been researched in full. System and structural, functional and legal comparative methods as well as systematization, analysis and synthesis were determinative in the research process.

However, most of Ukrainian scientists' articles were devoted to solving only certain problems in healthcare, in particular, such scientific materials covering issues of pharmaceutical activity [1; 2; 3; 4; 5; 6; 7] and fragmental matters in the field of health services [8].

REVIEW AND DISCUSSION

For understanding the impact of international medical law on the national law and legislation, it is worth to address the Constitution of the World Health Organization, which says that the primary objective of the organization shall be the attainment by all peoples of the highest possible level of health. The term "healthy" is understood, as specified in the Preamble of the Constitution, as a state of complete

physical, mental and social well-being and not merely the absence of disease or infirmity [9]. Exactly these provisions of the WHO Constitution are the basis of international medical law and determine its content. The development of the legal provisions which would contribute to improvement of health of all peoples on the planet in a most effective way is the major task of international medical law. International medical law is part of international law which regulates intergovernmental relations on issues of health care and medicine. Proceeding from this, international contracts and conventions, the provisions of which are aimed, first of all, at the improvement of health of peoples in peace-time and, in addition, to health care in case of war should be viewed as the sources for this field of law [10; 93].

The history of development of international legal provisions in health care is closely related to the domestic law aimed at health care of people and attempts to prevent spread of epidemics and infectious diseases. International legal provisions appeared later, their emergence was an objective necessity since separate states were unable to effectively combat epidemics [11; 262]. In the XXth century, with the development of medicine and international law there were plenty of international contracts and documents adopted. Some of them were of a complex character: along with the right of people to life and health care, they regulated some other relations (the Universal Declaration of Human Rights, 1948; the International Covenant on Economic, Social and Cultural Rights, 1966, etc.). Other documents only covered the issues of health care (the Declaration of Alma-Ata, 1978; the Ljubljana Charter on Reforming Health Care, 1996; the Declaration of Lisbon on Rights of the Patient, 1981, etc.).

The international documents on health care can be conditionally systematized by the following groups: 1) acts and documents characterizing the issue of reforming health care (the Declaration of Alma-Ata, the Ljubljana Charter on Reforming Health Care, etc.); 2) acts and documents, which outline the issue of participants' legal status in relations of health care (the Declaration of Lisbon on Rights of the Patient, the European Charter of Patients' Rights, the Declaration on Physician Independence and Professional Freedom, the Declaration on Human Rights and Individual Freedom of Medical Practitioners, the Position Statement on Nurses and Human Rights, etc.); 3) acts and documents, which touch upon specialized issues of medicine and health care (the Declaration on Euthanasia, the Declaration of Sidney (on death), the Principles for the Protection of Persons with Mental Illness and for the Improvement of Mental Health Care, the Universal Declaration on the Human Genome and Human Rights, etc.).

The analysis of implementation by Ukraine of the international position papers on reforming health care allow distinguishing a number of unsolved problems, which adversely affect the functioning of the Ukrainian healthcare system and proper exercise by the citizens of their constitutional right to health care. They are as follows:

1. The ethical and deontological constituents of health care are not provided now. Bioethics, which determines morality

of human conduct in biological and medical industry and in health care in terms of its conformity to the moral norms and values, is on the initial stage of development. In medical deontology, which is the set of ethics norms and principles of conduct of medical practitioners in professional accomplishments, there are numerous problems in implementation and adherence to these norms and principles. All the stated above adversely affect the activity efficiency of health care institutions and delivery of health care to the population. Some time ago, the Draft Law "On legal framework for bioethics and its ensuring guarantees" No 7625 dated June 8, 2005 was submitted for consideration to the Verkhovna Rada of Ukraine, but it was never adopted.

2. There are considerable difficulties in financing the health care reform. For a long time greater part of the budgetary financial support has been assigned for remuneration of health care institutions' staff and utility costs. There has been a serious funding shortfall for improvement of the material and technical condition of health care institutions and introduction of new treatment methods.

In order to implement the Concept of Health Care Reform ratified by the Order of the Cabinet of Ministers of Ukraine No 1013-r dated November 30, 2016 based on the economic situation and state of the healthcare system in Ukraine the Verkhovna Rada supported the health care reform on second reading and as a whole on October 19, 2017.

According to the Draft Law "On the state financial security of health care services and medications provision" No 6327 [12], the state guarantees payment for health care services and medications provided to patients (introduction of the principle "money follows the patient") fully or partly from the budget. It is important that guarantees should be provided without dependence on any additional criteria to all citizens of Ukraine, foreigners and stateless persons who reside permanently in the territory of Ukraine (first of all, to foreigners in families of Ukrainian citizens, persons formally recognized as refugees or persons in need of complementary protection).

The following provisions of the Law can be referred to as the essential ones: 1) introduction of the concept "package guaranteed by state" (a clearly specified amount of health care services and medications to be paid from the state budget); 2) full payment of medical services and medications for primary, urgent (approximately 80% of citizens' recourses) and palliative health care; partial payment of medical services on the secondary and tertiary levels; 3) payments of medical services and medications by state through the mechanism of public health care sharing; 4) insurance coverage from the state budget; 5) introduction of formal payment sharing for healthcare services delivery to insured persons from other sources in case of partial coverage of services cost; 6) treatment of persons insured in health care institutions of any ownership form; 7) performance of the functions of insurer and single strategic purchaser of health care services by the new central executive body – the National Health Service Ukraine ("NHSU"). The attention should be paid to the Draft Law of Ukraine "On additional financial state guarantees for provision of

health care services and medications to persons, who protect independence, sovereignty and territorial integrity in the anti-terror operation and ensure its performance” No 6328, which provides for state guarantees of full payment of any level treatment for participants of the anti-terror operation (“ATO”) [13] so that to admit their contribution and self-sacrifice in defence of Ukraine.

The above-stated and other innovations in medical industry represent a row of important changes both at the legislative level and at the level of health care and legal policies of the Ukrainian state. Firstly, the guarantees of healthcare services provision in general and those in relation to separate categories of persons in particular are expanded; secondly, the state encourages conscious activity and responsibility of citizens in relation to their attitude to own life and health (voluntary healthcare insurance); thirdly, recognition of international clinical directives for the purpose of applying the best world practices of healthcare services provision in Ukraine.

3. Unfortunately, the population’s needs in healthcare services in Ukraine are not satisfied. The evidence of this is insufficient financing and non-fulfilment of healthcare programs, namely: the National Social Target Program of Actions Against Tuberculosis for 2012-2016, the National Program of Fighting Against Oncology Diseases for 2007-2016, the State Target Program “Diabetes Mellitus” for 2009-2013, the National Program of Immunoprophylaxis and Protection of People from Infectious Diseases for 2007-2015 [14; 74].

In addition, the concept of the National Social Target Program of Actions Against Tuberculosis for 2012-2016 is still at a draft stage; the National Program of Fighting Against Oncology Diseases for 2007-2016 can only be adopted in 2018.

4. There is a low level of civic education in prophylaxis of diseases and healthy way of life. Currently there are no state-backed programs in this field and mainly public organizations are engaged in outreach. However, according to the statistical figures, civic education and promotion of discarding harmful habits (smoking, overweight, unhealthy diet) can considerably reduce the amount of cardiovascular diseases. Therefore, Ukrainian medicine should aim not only to treat but, first of all, to promote prophylaxis of diseases. However, these provisions remain non-enshrined in the legislation.

In the context of the above-stated group of problems attention should be paid to involvement of public organizations into actions against HIV and tuberculosis, including fulfilment of the state social order of providing health care to people with a limited access to medical services, increase in the level of public awareness, settlement of the problem related to negative attitude of society to patients with tuberculosis and HIV-positive persons and discrimination against them in the healthcare system. The strategy of advocacy, communication and social mobilization, assistance to creation of associations of people affected by these diseases and involving these people in fighting against them needs to be developed and introduced.

5. There is no legislative framework for family medicine. In the Fundamentals of the Legislation of Ukraine, there is Section III, which covers the issues of health care organization in Ukraine. In Articles 35 – 35-5 medical and preventive aid is divided into three types: primary, specialized (secondary) and highly specialized (tertiary) with elucidation of medical services amount provided at each level. But there is no concept of family medicine in the given Section. It can only be found in lower-level regulations – the Concept of Development of Health Care for the Population of Ukraine ratified by the Decree of the President of Ukraine No 1313/2000 dated December 7, 2000. Such a situation adversely affects the development of family medicine as a type of health care provision to the population.

6. The mechanisms of healthcare system management through independence of healthcare institutions are ineffective when managing own resources. Currently in Ukraine healthcare institutions of public and communal ownership cannot freely dispose of their money and mainly follow strict instructions “from superior bodies”. This situation adversely affects the efficiency of these institutions functioning. Now the Cabinet of Ministers of Ukraine has initiated the process of reforming healthcare industry, which includes autonomization of health care institutions, simplifies the process of hospital expenditures estimation, and also provides for creation of hospital regions for co-operation of hospitals and local self-government bodies. However, at the legislative level these changes are not enshrined in any law yet.

Thus, the domestic legislation and practice of its implementation in health care are characterized by some problems, their non-conformity to the international provisions and global practices of these provisions implementation. The numerous provisions of medical law adopted during the independence of Ukraine implement the legislative acts in accordance with the requirements of European integration. In some countries of the world – the USA, Italy, Spain, France and others – legal relations in health care are regulated by healthcare codes. Using this positive foreign experience, considerable part of the problem of healthcare legislative support in Ukraine can be solved through adopting of the codified legal act on health care.

In the context of the above said the opinion of I. Seniuta, who grounds the necessity of medical code development and adoption in Ukraine, is timely. She explains the urgency and importance of a codified act creation by the following circumstances: necessity to carry out a complex reform of the domestic healthcare system, including its legislative support as a ground for further transformations; current conformity of a science-based concept to the law-making activity in this field; aspiration for providing an increase of the legal knowledge level of medical practitioners; assistance and consulting provided by lawyers in considering and deciding of so-called “medical cases”; in some cases non-conformity of branch legislation to some laws on health care and medicine; need for clear regulation of medical practitioners and patients’ legal status; need for legal regulation of different healthcare systems (state, municipal, private) [15; 7].

Thus, adoption of the Medical Code is necessary for regulation of healthcare legislation in Ukraine and adaptation to the provisions of international and European standards. Harmonization and adaptation of healthcare legislation in Ukraine is a constituent in the process of European integration and legal globalization. There are some positive changes in the Ukrainian health care, namely the adoption of the Law of Ukraine “Fundamentals of the Legislation of Ukraine on Health Care” [16], which provides for the principles of healthcare activity in detail, though it has some gaps. This law is the basis, on which it is expedient to formulate suggestions for the content of the codified act.

For the countries of the Roman-German legal family, where Ukraine belongs to, the traditional structural organization of code is its division into General and Special Parts. The first part contains the basic provisions representing general and common legal provisions for the entire industry, which can be applied to all legal relations in health care. The second part contains the provisions, which are not universal and applied to specialized legal relations in health care.

Thus, the structure of the Medical Code may have the form as follows:

1. Section 1: the principles of medical law and definition of basic concepts.

2. Section 2: human and citizen rights in health care. The following list should be included in this part: the right of a person to qualified medical aid, safe natural environment, safe and healthy terms of labour, participation in law-making activity and management of health care, protection against any illegal forms of discrimination related to the state of health, etc. The legal status of patient should be defined separately, namely the definition of the term as well as patient's rights and obligations should be given, for instance, the right to consent or reject treatment, free choice of practitioner, methods of treatment and healthcare institution, right to obtain information on the state of health and the right to confidentiality of this information, right to receive educational information on healthy life styles, right to have their dignity and religious beliefs respected, right to appeal against wrongful decisions and actions of medical practitioners, healthcare institutions and bodies and right to compensation of damage done to the health.

3. Section III: legal status of medical practitioners. The rights of medical and pharmaceutical practitioners should include the following: execution of medical and pharmaceutical activity in accordance with speciality and qualification; right to proper conditions of professional activity and in-house training; compulsory insurance for the period of professional activity execution for the account of owner of healthcare institution, right to social aid from state, to defence of professional dignity, etc. As well, the given part should provide for the obligations of medical practitioners: to contribute to care and strengthening of people's health, prevention and treatment of diseases, to provide timely and qualified healthcare and medical aid; to provide emergency medical care in case of accidents and other extreme situations; to disseminate scientific and

medical knowledge among population and propagandize the healthy way of life; to adhere to the requirements of professional ethics and deontology, protect medical confidentiality; to constantly increase the level of professional knowledge and skill, etc.

4. Section IV: organization of the healthcare system. In this section special attention should be paid to family medicine as it is poorly regulated by legislation, but at the same time it should become the basic vector of development of medical services provision in Ukraine.

5. Section V: health care financing. The major issues, which require legislative revision, are the list of sources for financing health care and definition of certain autonomy for health care institutions in their authority over finances. These problems have been partly settled after the recent adoption of the Law of Ukraine “On making alterations to some legislative acts of Ukraine in relation to improvement of the legislation on issues of healthcare activity” dated April 6, 2017. However, the important innovation of medical insurance introduction has not been enshrined in the Ukrainian legislation, and the Code provisions should change the situation.

6. Section VI: standardization, control and supervision within the framework of healthcare activity. Sanitary and epidemiological welfare of the population, turnover of narcotic drugs and medications should become special objects of supervision and control.

7. Section VII: legal responsibility in medical law and provisions, which refer to other codified acts (The Code of Administrative Offences, Civil Code, Labour Code, Criminal Code).

8. Section VIII: international cooperation in health care – introduction of advanced technologies in treatment and rehabilitation of patients, use of foreign medications and health care reform in accordance with international standards.

The Special part of the Medical Code should include the sections defining the provisions of legal regulation of the following issues: pharmaceutical activity; expert activity; exercise of rights to reproduction and assisted reproductive technologies; blood and its components donorship, transplantation of organs and other anatomical materials; provision of sanitary and epidemic welfare, fight against infectious diseases; psychiatric aid; biomedical experiments on the person; cosmetology, sports medicine and health resort activities.

CONCLUSIONS

Summarizing the above-mentioned provisions, we can make the following conclusions. Most health care international acts are ratified by Ukraine and their provisions are implemented in the legislation. Simultaneously, there is a row of problems, which hinder the Ukrainian health care development and place obstacles in the way of European integration. To remove these obstacles, it is expedient to create a codified act – the Medical Code, which would systematize the provisions of the current medical laws and regulations and fill in the existing gaps in the legal

regulation of health care. Unfortunately, the introduction of international standards to the Ukrainian legislation does not mean that all the provisions will be accomplished in Ukraine indeed (but not in name) due to a lack of organizational or financial resources. Therefore, the primary objective of the processes of reforming the health care industry should be creation of the conditions under which the laws will be carried out and people of Ukraine will be able to exercise their inalienable right to health care in its entirety.

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Received: 02.10.2017

Accepted: 05.02.2018

ОСНОВНЫЕ НАПРАВЛЕНИЯ РЕФОРМИРОВАНИЯ СЛУЖБЫ МЕДИЦИНСКОЙ СТАТИСТИКИ В УКРАИНЕ

THE MAIN DIRECTIONS OF REFORMING THE SERVICE OF MEDICAL STATISTICS IN UKRAINE

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РЕЗЮМЕ

Введение: Реализация новых методов информационной поддержки принятия управленческих решений должна обеспечить эффективное реформирование системы здравоохранения и создать условия для улучшения качества оперативного управления, обоснованного планирования медицинской помощи и увеличения эффективности использования ресурсов системы. Реформирование службы медицинской статистики Украины необходимо рассматривать только в контексте реформирования всей системы здравоохранения.

Цель: данной работы является анализ существующей ситуации и обоснование основных направлений реформирования службы медицинской статистики Украины.

Материал и методы: В работе использован комплекс методов: контент-анализ, библиосемантический, системного подхода. Информационной базой стали: стратегические и программные документы ВОЗ, данные Центра медицинской статистики МЗ Украины.

Обзор: Служба медицинской статистики Украины имеет завершённую и действенную структуру, которую возглавляет Государственное учреждение «Центр медицинской статистики МЗ Украины». Именно данное учреждение отчитывается от имени МЗ Украины перед Государственной службой статистики Украины, Европейским бюро ВОЗ и другими международными организациями. Анализ существующей ситуации показал, что для достижения поставленной цели является необходимым: усовершенствование системы статистических показателей для адекватной оценки результатов деятельности учреждений здравоохранения, в том числе в экономическом аспекте; создание развитой медико-статистической базы административных территорий; изменение существующих технологий формирования информационных ресурсов; укрепление материально-технической базы структурных подразделений службы медицинской статистики; совершенствование системы подготовки и переподготовки кадров для службы медицинской статистики; развитие международного сотрудничества в области методологии и практики медицинской статистики, внедрение общепринятых в международной практике методов сбора, обработки, анализа и распространения медико-статистической информации; создание медико-статистической службы, адаптированной к особенностям рыночных отношений в здравоохранении, гибкой и чувствительной к изменениям в международных методологиях и стандартах.

Выводы: Данные медицинской статистики лежат в основе принятия управленческих решений руководителями всех уровней здравоохранения. Реформирование службы медицинской статистики Украины необходимо рассматривать только в контексте реформирования всей системы здравоохранения. Основными направлениями реформирования службы медицинской статистики в Украине является: внедрение информационных технологий, совершенствование подготовки кадров для службы, улучшение материально-технического оснащения, максимальное повторное использование полученных данных, что предусматривает унификацию первичных данных и системы показателей. Наиболее сложным направлением является формирование информационных фондов и внедрение современных информационных технологий.

КЛЮЧЕВЫЕ СЛОВА: медицинская статистика, управление здравоохранением.

ABSTRACT

Introduction: Implementation of new methods of information support of managerial decision-making should ensure of the effective health system reform and create conditions for improving the quality of operational management, reasonable planning of medical care and increasing the efficiency of the use of system resources. Reforming of Medical Statistics Service of Ukraine should be considered only in the context of the reform of the entire health system.

The aim: This work is an analysis of the current situation and justification of the main directions of reforming of Medical Statistics Service of Ukraine.

Material and methods: In the work is used a range of methods: content analysis, bibliosemantic, systematic approach. The information base of the research became: WHO strategic and program documents, data of the Medical Statistics Center of the Ministry of Health of Ukraine.

Review: The Medical Statistics Service of Ukraine has a completed and effective structure, headed by the State Institution "Medical Statistics Center of the Ministry of Health of Ukraine." This institution reports on behalf of the Ministry of Health of Ukraine to the State Statistical Service of Ukraine, the WHO European Office and other international organizations. An analysis of the current situation showed that to achieve this goal it is necessary: to improve the system of statistical indicators for an adequate assessment of the performance of health institutions, including in the economic aspect; creation of a developed medical and statistical base of administrative territories; change of existing

technologies for the formation of information resources; strengthening the material-technical base of the structural units of Medical Statistics Service; improvement of the system of training and retraining of personnel for the service of medical statistics; development of international cooperation in the field of methodology and practice of medical statistics, implementation of internationally accepted methods for collecting, processing, analyzing and disseminating medical and statistical information; the creation of a medical and statistical service that adapted to the specifics of market relations in health care, flexible and sensitive to changes in international methodologies and standards

Conclusions: The data of medical statistics are the basis for taking managerial decisions by managers at all levels of health care. Reform of Medical Statistics Service of Ukraine should be considered only in the context of the reform of the entire health system. The main directions of the reform of the medical statistics service in Ukraine are: the introduction of information technologies, the improvement of the training of personnel for the service, the improvement of material and technical equipment, the maximum reuse of the data obtained, which provides for the unification of primary data and a system of indicators. The most difficult area is the formation of information funds and the introduction of modern information technologies.

KEY WORDS: medical statistics, health care management

Wiad Lek 2018, 71, 1 cz. II, 207-210

ВВЕДЕНИЕ

В условиях реформирования системы здравоохранения органы управления отраслью, как никогда, нуждаются в получении качественной, достоверной и своевременной информации о состоянии здоровья населения и работы лечебно-профилактических учреждений. Неоспорим тот факт, что от качества сбора, хранения и обработки информации зависит правильность принятия управленческого решения на разных уровнях управления [1,2].

Реализация новых методов информационной поддержки принятия управленческих решений должна обеспечить эффективное реформирование системы здравоохранения и создать условия для улучшения качества оперативного управления, обоснованного планирования медицинской помощи и увеличения эффективности использования ресурсов системы [5,6] Реформирование службы медицинской статистики Украины необходимо рассматривать только в контексте реформирования всей системы здравоохранения. Вместе с тем, за время независимости Украины уже было столько попыток реформировать систему здравоохранения. Поэтому может и хорошо, что служба медицинской статистики не была втянута в этот непредсказуемый водоворот событий [3,4].

ЦЕЛЬ ИССЛЕДОВАНИЯ

Целью данной работы является анализ существующей ситуации и обоснование основных направлений реформирования службы медицинской статистики Украины.

МАТЕРИАЛ И МЕТОДЫ ИССЛЕДОВАНИЯ

В работе использован комплекс методов: контент-анализ, библиосемантический, системного подхода. Информационной базой стали: стратегические и программные документы ВОЗ, данные Центра медицинской статистики МЗ Украины.

ОБЗОР И ОБСУЖДЕНИЕ

Служба медицинской статистики Украины формировалась на остатках советской статистики, но со временем начала структурироваться в самостоятельную службу со своими специфическими задачами и своей нормативно-правовой базой.

Приказ Министерства здравоохранения от 05.10.98 №292 «Об утверждении Программы реформирования медицинской статистики», в котором были очерчены как концепция Программы, так и конкретные меры по ее выполнению, положил начало собственно процессу реформирования службы медицинской статистики. Целью реформы стало повышение роли службы в улучшении управления здравоохранением и завершение перехода на международную систему учета и статистики. Выполнение вышеупомянутой Программы фактически позволило создать структуру службы, которая работает и по сей день.

На сегодня, в каждой области есть свой областной информационно-аналитический центр медицинской статистики, а в каждом лечебном учреждении - информационно-аналитический отдел. Возглавляет службу Государственное учреждение «Центр медицинской статистики МЗ Украины». Именно данное учреждение отчитывается от имени МЗ Украины перед Государственной службой статистики Украины, Европейским бюро ВОЗ и другими международными организациями.

Существующая структура службы позволяет не только собирать, обрабатывать и хранить медицинскую статистическую информацию, областные информационно-аналитические центры медицинской статистики на местах выполняют гораздо больше функций, в зависимости от задач, возложенных на них местными властями. Это может быть участие в аккредитации учреждений здравоохранения, внедрение и сопровождение современных информационных приложений, юридическая поддержка принятия управленческих решений на областном уровне и тому подобное.

Вопрос о реформе структуры службы медицинской статистики станет еще более актуальным после внедрения современных информационных технологий в повседневную жизнь учреждений здравоохранения и врачей, а также после настоящего полномасштабного реформирования системы здравоохранения Украины [2].

Реформирование службы ведется в двух направлениях: перестройка структуры и ресурсов, а также изменение в учетно-отчетной документации.

К ресурсам медицинской статистики, в первую очередь, относятся кадры, а также техническое и программное обеспечение.

Врачи-статистики и врачи-методисты относятся к категории врачей-организаторов здравоохранения, они осуществляют руководство медицинскими статистиками, организуют статистический учет, контроль, сводку и анализ медико-статистической информации в учреждениях здравоохранения.

В службе медицинской статистики, в последние годы, задействовано 905 врачей и 184 специалистов с высшим немедицинским образованием, а также 4258 средних медицинских статистиков. Подготовка и переподготовка врачей и специалистов с высшим немедицинским образованием происходит на кафедре медицинской статистики Национальной медицинской академии последиplomного образования имени П.Л. Шурика, а медицинские статистики проходят обучение на базе учебных заведений 1-2 уровней аккредитации.

Эффективность деятельности службы медицинской статистики зависит не только от совершенства ее организационной и функциональной структур, но и от состояния ее информационной системы. Внедрение в систему здравоохранения современных информационных технологий, безусловно, повлияет на численность работающих в службе медицинской статистики. Чем шире современные приложения будут использоваться в учреждениях здравоохранения, тем меньше рутинной работы будет оставаться, а достоверность статистической информации будет расти. Вместе с тем, аналитическая работа всегда будет нужна как руководителям здравоохранения, так и работникам новой службы, которая только зарождается в Украине - службы общественного здоровья. То есть, независимо от того, как будет называться должность - врач-статистик, врач-методист или врач-аналитик, такая работа будет нужна и в будущем.

Внедрение современных информационных технологий в работу всей системы здравоохранения, то есть введение в полном объеме системы электронной охраны здоровья (e-health) является наиболее перспективным, но и наиболее сложным и дорогостоящим.

Сегодня информационная система службы медицинской статистики, в основном, базируется на прикладном программном обеспечении «Медстат». Программа «Медстат» используется с 1994 года и уже выдержала несколько обновлений и доказала свою эффективность и жизнеспособность. Более двух десятилетий медицинские статистические отчетные формы обра-

батываются с помощью указанной программы как в областных информационно-аналитических центрах медицинской статистики, так и в ГУ «Центр медицинской статистики МЗ Украины». На фоне постоянного изменения, расширения и обновления отчетных форм ежегодно обновляется и программа «Медстат» с дальнейшим направлением ее в регионы за несколько месяцев до наступления отчетов.

Кроме программы «Медстат», в учреждениях здравоохранения широко применяются прикладные программные комплексы типа «Поликлиника» и «Стационар», которые в автоматическом режиме формируют из учетных статистических форм отчетные, а также реализуют обработку других видов информации - научной, административной, клинической. Таким образом, управленческая деятельность руководителей здравоохранения различных уровней управления (республиканского, областного, районного, городского) обеспечивается, в основном комплексами задач, которые реализуются соответствующими уровнями службы медицинской статистики.

Стоящие перед государством задачи в области здравоохранения, а также интеграция в европейское сообщество привели к увеличению спроса на медицинскую статистическую информацию. Именно реформирование службы медицинской статистики должно обеспечить достаточность статистических данных для управления здравоохранением.

Пути реформирования службы обусловлены требованиями ВОЗ и фактом присоединения к странам с развитыми медицинскими информационными системами, что предусматривает следующие шаги:

- усовершенствование системы статистических показателей, которые адекватно отображают результаты деятельности учреждений здравоохранения, в том числе в экономическом аспекте;
 - создание развитой медико-статистической базы административных территорий;
 - изменение существующих технологий формирования информационных ресурсов;
 - укрепление материально-технической базы структурных подразделений службы медицинской статистики;
 - совершенствование системы подготовки и переподготовки кадров для службы медицинской статистики;
 - развитие международного сотрудничества в области методологии и практики медицинской статистики, внедрении общепринятых в международной практике методов сбора, обработки, анализа и распространения медико-статистической информации;
 - создание медико-статистической службы, адаптированной к особенностям рыночных отношений в здравоохранении, гибкой и чувствительной к изменениям в международных методологиях и стандартах.
- Реформа системы статистических показателей предусматривает создание целостной, динамической и обоснованной системы. Оптимальный перечень

статистических показателей должен удовлетворять потребности всех пользователей информации - от руководителей и фармпроизводителей до обычных граждан Украины. Но именно в этом и есть сложность. Так как невозможно непрерывно увеличивать количество информации, необходимой для расчета статистических показателей. Это связано как с большими ресурсными затратами, так и с тем, что (по данным Евростата) продуктивно используется только пять процентов информации от тех объемов, которые собираются. Не следует ожидать улучшения качества статистической информации от увеличения объемов или ограничения использования существующих данных, надеясь на улучшение надежности и качества.

На наш взгляд, решение проблемы заключается в том, чтобы сделать существующие данные более доступными и пригодными для анализа, чтобы конкретные пользователи должным образом могли воспользоваться возможностями, которые предоставляют современные информационные технологии.

Опыт показывает, что более широкое использование уже имеющихся данных является мощным стимулом для повышения их надежности и качества. От наличия скоординированного и удобного для пользователей доступа к широкому кругу разнообразных данных о ресурсах здравоохранения и состоянии здоровья населения зависит повышение эффективности служб здравоохранения.

Реформа системы статистических показателей должна предусматривать реализацию современных подходов к организации статистического учета (новые формы статистического наблюдения, отчетности, отказ от показателей, которые потеряли актуальность и т.д.). Система показателей должна способствовать повышению практической значимости и аналитической ценности информации для всех уровней управления здравоохранением.

На сегодня система медицинских статистических показателей базируется на учетных статистических формах, которые используются в различных учреждениях. Таких форм в здравоохранении уже около семисот. Неоправданно большое количество учетных форм создает огромную нагрузку на врачей и медицинских сестер, отвлекая их от выполнения своей основной деятельности. В последние годы Министерство здравоохранения Украины позволило вести почти все учетные формы в электронном виде, но это только первый шаг на пути внедрения современных информационных технологий в деятельность учреждений здравоохранения. Следующим логическим шагом должно стать утверждение унифицированной электронной учетной формы, которую можно будет использовать как в амбулаторных, так и в стационарных учреждениях здравоохранения, то есть на всех уровнях оказания медицинской помощи.

Вместе с тем, необходимо осознавать, что реформирование системы статистических показателей может

привести к потере преемственности в некоторых динамических сопоставлениях.

Одним из важных направлений реформирования медицинской статистики Украины становится внедрение системы государственных классификаторов и реестров. Реорганизация системы медицинской статистики требует продолжения построения системы классификации и кодирования медико-статистической информации, основной частью которой является система классификаций, гармонизированных с международными классификациями. Речь идет не только о международных статистических классификациях, но и о международных клинических классификациях, внедрение которых позволяет говорить с развитым миром на одном языке. Сюда следует отнести также введение в Украине системы диагностически-связанных групп (DRG), которая развивается сравнительно недавно [8].

Наиболее сложным направлением реформирования медицинской статистики в Украине является формирование информационных фондов и внедрение современных информационных технологий. Основным результатом внедрения этого «этапа реформирования» должен быть переход на комплексную технологию сбора, обработки, передачи, накопления, анализа и отображения статистической информации. Но внедрение этого этапа зависит от состояния внедрения электронного здравоохранения в целом, поскольку концепция электронного здравоохранения должна включать в себя создание современных информационных ресурсов, а не наоборот. Введение в Украине только одного из важных компонентов электронного здравоохранения, а именно - электронного реестра пациентов, уже принципиально изменит процесс формирования информационных медицинских фондов. Вместе с тем, создание электронного реестра пациентов Украины требует финансовых затрат, которые исчисляются миллиардами гривен, что весьма проблематично в современных экономических условиях.

Переход от бумажных к электронным носителям информации в здравоохранении Украины уже начался и только вопрос времени - когда он состоится в полном объеме. Врачи-статистики заинтересованы в этом процессе больше, чем представители других медицинских специальностей, поскольку цель их работы - повышение достоверности статистической информации. Вместе с тем, в современном беспокойном мире все больше требований предъявляется к защите персональных данных. Следует понимать, что защита персональных данных в значительной степени удорожает стоимость тех прикладных программных продуктов, которые используются для создания электронного реестра пациентов. И хотя медицинская статистика в основном использует обезличенные данные, торможение процессов внедрения современных информационных технологий в здравоохранение негативно влияет на ее развитие.

ВЫВОДЫ

Данные статистики лежат в основе принятия управленческих решений руководителями всех уровней.

Реформирование службы медицинской статистики Украины необходимо рассматривать только в контексте реформирования всей системы здравоохранения.

Основными направлениями реформирования службы медицинской статистики в Украине является: внедрение информационных технологий, совершенствование подготовки кадров для службы, улучшение материально-технического оснащения, максимальное повторное использование полученных данных, что предусматривает унификация первичных данных и системы показателей.

Наиболее сложным направлением реформирования медицинской статистики является формирование информационных фондов и внедрение современных информационных технологий.

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Прислана: 22.08.2017

Утверждена: 25.01.2018

FACTORS OF THE MEDICAL CAREER CHOICE WITHIN THE CONTEXT OF UKRAINIAN HEALTHCARE REFORMS

CZYNNIKI WPŁYWAJĄCE NA WYBÓR ZAWODU LEKARZA W KONTEKŚCIE REFORM OCHRONY ZDROWIA ZACHODZĄCYCH NA UKRAINIE

Lesia Lymar, Sergii Omelchuk

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ABSTRACT

Introduction: The article is dedicated to the motives of medical career choice studied by Ukrainian and foreign scientists, and by the authors themselves. The authors define the main motives, grouped into the pragmatic, social, scientific and professional ones, paying particular attention to the proposed reforms of the Healthcare of Ukraine "Health 2020".

The aim: The study has been aimed at detection of the medical career choice factor groups and their possible correction during the medical training, defining possible influence of the Ukrainian Healthcare reformation onto alterations of the medical career choice.

Materials and methods: This article is based on bibliosemantic, dialectical, comparative, analytic, synthetic and comprehensive research methods.

Review and conclusion: The authors have analyzed medical career motives according to the A. Maslow hierarchy of needs, comparing the present motives with the motives to be changed after reforming the Ukrainian healthcare. The authors conclude that according to the Maslow's hierarchy of needs, the medical career choice corresponding to the first, second and third needs level would be directly related to the pragmatic, social and scientific motives, further disappointment in career, low professional performance and professional "burnout". The career choice corresponding to the last levels of the needs hierarchy is related to the professional motives and self-actualization, but, due to the applicants' age and financial status of medical specialists in Ukraine, is not likely to occur. Positive changes in medical specialists' salary rise, social protection offered by the State and state support of the profession will provide for correction of motives onto the higher level, in this way, benefiting the patients.

KEY WORDS: Medical education research – management, profession, medicine –profession, student support, public health

Wiad Lek 2018, 71, 1 cz. II, 211-216

INTRODUCTION

There are many factors which provide for high competitive performance of the Ukrainian medical specialists on the world medical market, including professional knowledge, skills and effective "physician-patient" interaction abilities aimed at recovery of the last and practically implemented. The successful interaction of a physician and a patient is closely related to the professional activity motives, which, in turn, are related to the career choice motives. The aims of the "physician-patient" interaction stipulate for the effectiveness of the interaction, aimed at the patient's recovery. Medical career choice motives may be classified into the primary and secondary ones. The primary motives are represented with the motives of the career choice when a person chooses the university to apply for, while the secondary motives may alter throughout the training and practice. So, it is extremely important to detect the primary motivation during the student's training in a medical school, and, if necessary, to correct the motives before one starts his career. The Health care system of Ukraine is undergoing reformation changes, with the claimed-to-be high social position of the medical specialists, high salary

and social protection of doctors as well as general transformation of the "physician-patient" interaction structure [1]. The expected changes could affect medical career choice motives. As the issue of the medical career choice is particularly urgent in Ukraine in 2017, regarding the medical social position changes and the State guarantees, promised by new reforms, we have made up our mind to study this topic throughout.

THE AIM

The study has been aimed at detection of the medical career choice factor groups and their possible correction during the medical training, defining possible influence of the Ukrainian Healthcare reformation onto alterations of the medical career choice.

MATERIALS AND METHODS

This article is based on bibliosemantic, dialectical, comparative, analytic, synthetic and comprehensive research methods.

REVIEW AND DISCUSSION

The issue of medical career choice motives and medical interaction motives has been studied by many Ukrainian and world healthcare specialists: K. Mikhno [2], I. Vitenko [3], L. Lymar [4], S. Omelchuk [5], I. Pasichnyk [6], K. Pivtorak [7], T. Rumiantseva [8], M. Morgan [9], D. Sobral [10], R. Tyssen [11] and others. The career choice by the school graduates issue has been investigated by R. Ovcharova [12], Ya. Tsekhmister [13], R. Kuzurkar [14]. The career choice motives of the nurses are the topic of studies by Ye. Kadnikova [15], V. Ruban [16]. L. Crossley and A. Mubarik compared the career choice motives of the medical students and dental students [17]. L. Lymar [4], K. Pivtorak [7] and T. Rumiantseva [8] have studied transformation of the medical career choice motives during the medical students' training. I. Pasichnik [6], M. Morgan [9] and I. Wang [18] emphasized general medical image structure and related to this the medical career motivation. Some authors regard career choice motivation as a component of professional self-identification, while others consider it as a component of the emotions and will of a personality. According to A. Perepelytsa, the professional self-identification and career choice motives represent combination of moral values of the person, attitude to the career, plans of the person regarding the career and their correction according to the career image [19]. K. Pivtorak stresses upon the direct relation of the medical career choice motives and the person's moral and ethical values [7]. V. Ruban notes that the professional "burnout" is a main factor which may alter the person's career choice motives [16]. L. Lymar claims that the medical students' career choice motives guarantee the effectiveness and productivity of the "physician-patient" interaction and the treatment outcome [5]. I. Pasichnyk correlates the career choice motives to the general medical career image [6]. Regarding all the studies, the authors have decided to analyze the present medical career choice motives according to the personality structure by Freud, and classify the motives according to the A. Maslow pyramid.

The professional's performance depends on his readiness for the professional interaction. The previous analysis performed by L. Lymar, established the following components of the professional interaction readiness: motives, cognition, operation and regulation [4]. Motives take up priority position as the professional interaction motives stipulate for all other components as their causing factor. The motives of the medical specialist for the professional interaction comprise the sub-components, such as: medical career choice motives, motives of professional growth and motives of professional interaction. The career choice motives represent the primary component of the professional interaction motives, which defines general motives for the professional activity. According to the performed review of the literature data and the personal medical school teaching experience of the authors, the career choice motivation has been defined as a group of motives which caused the person to choose the desired career path and try hard to acquire the appropriate qualification.

Combination of the medical career choice motives represents the system of attitudes of the person to the chosen

career, professional activity and interaction with the others (both medical specialists and non-medical people) during execution of the professional duties as well as the system of attitude of the friends, relatives and other people. Due to the authors' personal teaching experience in the Medical school, the following medical career choice motives have been established: the forced choice "against the will of a student" (when the parents want their child to become a doctor, but the person doesn't want it); forced choice, the student willingly accepting it; career prestige; possibility to earn good money; way to receive the respect of the others; possibility to save the other's lives; nice portrayal of the career in mass media; student's personal interest in medicine as a subject; possibility to become world famous as a genius physician; person's admiration of his physicians he knows; unconscious career choice, the choice "due to the circumstances" (explained as "it simply happened so..."), etc. Generally, the all career choice motives may be classified into the internal ones (direct motives of a certain person, with the defined influential factors) and the external ones, which may be conscious (the career chosen on the parents' decision, when the person wants to choose another profession) and non-conscious (choosing the career because "it is well portrayed", "the friends or parents advised me", without certain self-realization of its necessity).

The medical career choice motives may be grouped as follows:

- pragmatic motives: obtaining any material benefits ("profitable career"), career ladder possibilities, social assertion through the fame; taking up the authority position in medicine, running a clinic, etc. The student chooses medical profession for the high medical salary (choosing in Ukraine specialties like gynecology or plastic surgery, with which one can be employed in a private clinic and be paid better than the state physicians, receiving about 100 American dollars a month). The other career choice motives are one's possibility to step up the career ladder and take up the administrative authority positions (which is quite often in Ukraine observed in medical dynasties, with parents and children engaged in one field of the medicine, or when the parents manage the private clinic and their son or daughter, upon graduating from the University, will run the clinic). Another motive from this group is one's desire to become world famous through being a good specialist, being able to perform operations no one else can do or discovering a new treatment method. If this motive group predominates, the students, upon their University graduation, will try to avoid being "directed by University to their first workplace" to the suburbs regions, which could bring them neither money nor fame; neglecting the non-prestigious specialties, which don't provide for any additional benefits (like a career of a family physician, being nowadays very demanding but little paid). With this motive group prevailing the students try to neglect their employment on the distant regions of the country (which results in lack of medical specialists in rural regions, which is an urgent problem for Ukraine) and avoid non-prestigious specializations.

- social motives, including possibility of direct communication with patients and their relatives, self-representation before their patients and their relatives, etc. The students claim to have chosen the career because they “like helping others”, “love children” (pediatric students), “love communication”, or “This is going to be a funny and interesting career”. The medical career here is perceived as an entertainment method, the way to avoid the life boredom, quite often chosen by the extraverted people to provide for broad communication possibilities, by people with low self-esteem or high self-esteem, when the professional activity of a physician provides for personal self-representation.
- professional motives, including providing good patient’s health, improving his health (though, there are some hidden benefits in these motives, such as self-representation of a talented physician, which is confirmed by a patient’s recovery, that is, healing the patient to prove doctor’s professional qualities, heal the patient to become known and famous, etc.. In this case the submotives of the career choice need to be regarded carefully).
- scientific motives including career choice in order to contribute to the science and become respected in it. This excludes the patient from the professional interaction chain, which may be beneficial for the laboratory specialties (specialties of a microbiologist, virologist, etc.), with which the medical specialist doesn’t have to communicate with the patient. The danger of such choice may be manifested in neglecting patient’s welfare for the sake of one’s scientific reputation. This group is quite interesting as such motives may express one’s interest in the whole medical science or be the pragmatic motives (discovering a new method provides a basis for becoming world famous and rich), or represent the way to rationalize the choice caused by other conscious or unconscious factors.
- motives of personal self-actualization, including professional self-actualization, learning new methods of managing the medical tasks and interaction. These motives may be stipulated for the person’s interest in the specialty or both pragmatic and social motives, though being the most appropriate when defining doctor’s motivation.

The medical career choice is usually based on many motives, and this combination of motives defines this choice, although one or two motives predominate. When a certain motives group prevails (e.g., tendency to receive certain material benefits, or acquiring new knowledge and skills after the practice), this may substantially limit the physician’s activity scope. At the same time, it is extremely important for the specialist to realize the importance of his own career choice motives.

In this article we have tried to consider the psychological essence of the career choice motives, particularly in Ukraine. Defining motives due to the personal structure according to Z. Freud, the following observations are offered: positive and nice mass media portrayal of medical professions provides for such motives of medical career choice, according to the unreal “ideal ego” structure, with high expectations from it, that a person tries to compensate for his own imperfectness,

trying to be the best, saving others’ lives and, in this way, substituting the God. Considering the average age of the medical schools applicants, which in Ukraine is 17-18 years (after finishing secondary schools usually), with prolonged teenager crisis and immature moral values, undergoing separation from the parents (and trying to prove them something or at least be equal with them), combines with the youth black-and-white thinking(tendency to be the best and save the world), it is possible to deduce that the medical career choice in this age is well grounded as the choice of the “best career” in the world or possibility to “change the world”. Though, in a few years period the psychic structure of the personality may change, with motives changing as well. If the person hasn’t shaped his “ego” concept, not realizing one’s own wishes, both internal and external needs, he may become severely frustrated in the profession, while meeting with practice. In addition, practice and emotional “burnout” change the career choice motives as well. So, to improve doctor’s professional performance, during the Medical School training it is necessary to define one’s motivation, structure of “ego real” and “ego ideal”, and shape the “ego professional” which will be based upon the “ego real”. The tasks of the Psychological Department of the Medical School and Educational Department include defining the motives and general psychic structure of the future specialists, with its subsequent correction during the medical studies.

Motivation of any activity originates in the needs. In the article we relate medical career choice motives to the A. Maslow hierarchy of needs (which is a universal reflection of the human needs) [20]. The first stage of the hierarchy is represented with basic physical needs: satisfying the thirst, hunger, etc. the second stage is represented with the need of safety, which are relatively “higher” needs: safety provided though provided accommodation, occupation, safety around, regular income and social guarantees, etc. If both two stages are provided to a person, he develops needs of the third stage: the need to belong to the community, to be well received by the others, etc. The next stage is the need for respect and fame, recognition. The last stage is manifested with the need for self-actualization, searching for one’s position in life and aims of life. Hereafter we are going to consider the medical career choice motives according to the A. Maslow hierarchy of needs.

A person, whose actual needs are those of the first hierarchy stage, will choose the medical career with only pragmatic motives, e.g. choose the profession to earn a living, decide the accommodation problem(living in a hostel for doctors or obtain the social accommodation), etc. So, if the problem of accommodation is urgent, or a person’s family belongs to the low income group, he will choose medical career only with pragmatic motives. Standardly, physiological needs of the 1st stage must be provided for at least 85%, otherwise all activity of a person is aimed just at surviving. This is the primary factor, not regarding some unpleasant profession peculiarities(like deaths of the patients and responsibility of a doctor). For those, choosing the medical career only with the pragmatic motives, having encountered with the state medical salaries

for those who start practice(which in 2017 range from 100 to 150 American dollars, according to the currency exchange), frustration in the career is inevitable, which may result either in changing the profession (and giving up medicine at all), or just pragmatic attitude to professional duties, when all the person's activities are aimed at earning money. No motivation correction measures will be effective, unless the physiological needs of a specialist (provided with clothes, food and accommodation) are satisfied. Here Medical School may raise a person's motives for studying though the grants and scholarships, though with insufficiently provided material needs other motives can be slowly shaped. If, according to the scheme of reforms, medical specialists will be provided with accommodation and appropriate salaries [21], Medical School Psychological Department, Medical School Educational Department and Medical Institutions Administration may cooperate to alter secondary career choice motivation, shifting it from the pragmatic motives only. If, according to the reforms scheme, medical specialists salaries will increase, compared to the nowadays, and the specialist's basic needs are provided (or a medical student realizes that upon his graduation all his basic needs will be covered by a state salary), motives of the career choice and professional interaction may "shift" onto the second stage of the needs hierarchy, to the personal self-representation, receiving the respect and self-realization, which would be more productive for the professional performance.

The second stage of the needs, needs for safety, are represented with the permanent job place, social guarantees, sick leave, social accommodation, related to the pragmatic and social motives of the career choice. A person choose medical career as the reliable one, which will provide him with certain social benefits. One may choose the career for treating himself or his own family, which may be related to unsuccessful history of treatment on the family, or due to a personal fear of being ill. The safety is realized through provision of physiological needs and certain social guarantees of the employer. So, in Ukraine, graduates often choose to work as medical representatives of large pharmaceutical companies (not as medical specialists!), due to high social guarantees (insurance, provision with private transport, compensations, financial support of the employees, credit line). If state supports graduates with the same on state positions, particularly family doctors (which is a specialty avoided by most graduates due to high responsibility, absent specialization and low social protection), the problem of specialists insufficiency will be solved.

The career choice with the second stage of motives is a more conscious choice than the previous one, but it is still far from dedication to medicine. According to the standard, safety needs must be provided for 70%, otherwise a person will experience fear and tension, and all decisions made by a person will be affected by the fear. I.e., if a person understands, that practice with the ambulance brigade won't support his financial needs, ambulance system may be terminated (according to the reforms, medical specialists in the ambulance vehicles to be changed by paramed-

ics without medical education), or that his educational certificate can't guarantee him employment in the wished field, on this stage he will leave the medical career, deciding on the both first (pragmatic) and second stages of the needs. Apart from this, military actions on the territory of Ukraine provide for another anxiety reason, conscious or unconscious, leading to the medical career choice for protection of oneself. It is necessary to support the students during their medical training, explain them the standards and laws concerning their employment combined with psychological consultations on the student's anxiety level, to correct the need for safety, so the profession career choice will be aimed at the patient's welfare. Health care reforms and social support of medical specialists will provide for the altered career choice motives from this stage, but the state support will fulfill the second stage needs, leading to the more high stage of the career choice motives.

After the basic issues of accommodation, food and permanent job, the next need stage of a person is the need for socialization. This is manifested in "belonging" to the certain medical society or working in a definite group. These needs stipulate for the social motives of choice: interaction with patients; and the social-pragmatic ones: being employed in a prestigious clinic, choosing the profession due to its mass media image, meeting new people, etc. These motives aren't related to the patient's welfare, but to the doctor's self-representation. Poor social acceptance of a person, absence of friends, low social background of the person's family lead to the shifted motives, in order to "prove", "step up on the higher social ladder stage", "realize oneself through the career", forgetting about the main task of the physician –interaction and treatment of the patient. E.g., a person may be so greatly overwhelmed with a doctor's role, medical interaction with patients and their relatives and being in the medical society, that he forgets about his main tasks. Another motive of the medical career choice from this stage is substituting one's personal family with a professional "family" (which occurs in case of problems in family and absent communication with the parents). What Medical School Service can do in the situation is to detect psychological peculiarities of a student and correct them (managing problems of introverted and extroverted students, family relations, etc.). According to the U. Suprun's, acting as a Minister of Health Care of Ukraine, interview to the Ukrainian medical Bulletin, Ukrainian medical specialists must be respected the same as in the other countries of Europe and world [22], which will be achieved through reforming the healthcare system. Implementing the reforms will shift the main needs focus onto the upper stage, appropriate not to the pragmatic motives, but social, scientific and practical ones.

The next hierarchy level is the need for fame and recognition. The motives of this stage are the pragmatic, scientific and social, with the specialist striving to be recognized by the others, sometimes neglecting human factor in his interaction with patients. These motives prevail in some cases: with unsatisfied first and second stages of the pyramid, a person covers for the unsatisfied

physiological needs and safety needs, trying to get “most from the job”. Or this may be observed in medical dynasties, when a person is used to the positive image of his surname (as the parents are well-recognized specialists), or when the parents since early childhood say to a person that he will be a famous doctor. Unfortunately, the patient’s welfare is neglected here, as this is not the main career and professional activity choice factor. Educational Department of Medical School is responsible for defining students’ needs of this stage and correct motives through active professional practice, participation in the students’ self-organization, etc. During 6 years of medical studies in Ukraine each student has an opportunity to fulfill his primary needs in recognition or alter the career choice motives in respect to the need, otherwise, continuing his practice to be recognized by the others.

The last stage of the Maslow hierarchy is the need for self-actualization, searching for one’s destination, life position, which almost coincides with the altruistic career choice. This may be realized with the previously developed and satisfied lower stages of needs, e.g. when a person is provided with finances, his family receives social support from the state, a person is well respected by the background, etc. As for the functions of the Medical School regarding last stage of the hierarchy, choosing medicine as a career from the last stage of needs is the direct task of Medical School, provided by permanent and continuous follow-up of the student throughout all 6 years of medical studies (and the subsequent years of internship and specialization). What provides for the career choice from the last needs stage is: educational and professional mobility of the students and medical specialists, high competitiveness of Ukrainian specialists in the world market of medical services, possibility to engage in one’s own private practice (starting with the private family doctor practice and finishing with a private clinic), supported by the state credit lines. And such career choice is the most productive for the physician’s self-actualization, on both personal and professional levels, providing for high professional performance.

So, theoretically the morally mature medical career choice is possible to be made by an adult person, who isn’t undergoing the age crisis, having realized oneself in certain life spheres (which is possible is a person is financially and socially supported by the state), and all this corresponds to the claimed by the state reform trends. As the average age of the medical career choice in Ukraine makes up 17-18 years (after finishing secondary school) and at this age many personal characteristics of the applicants aren’t shaped yet, the career choice can’t be stipulated for the last stages of the hierarchy, but may correspond to the 1st or 2nd stages or be externally forced. So, the educational aims of the Medical schools and Medical Institutions include defining the person’s motives of the career choice, their needs, correcting the motives and satisfying the needs, which is only possible with close interaction of the medical schools and healthcare system. The educational measures will be effective only

if the specialist’s needs are supported by the healthcare system, being the main employer in Ukraine. So, the tasks of the state and Ministry of healthcare of Ukraine include total financial, social and spiritual support of the medical specialists, raising the respect for medical profession, and increasing the competitiveness of the Ukrainian specialists on the world labour market, which will provide for higher medical career motivation.

CONCLUSIONS

Medical career motivation is represented with a group of motives which caused a person to choose a certain medical specialty and try to obtain the qualification. Personal experience of the authors provided for classifying career choice motives into the internal (conscious career choice) and external ones (both conscious and non-conscious career choice, forced from outside). Analysis of the main medical career choice factors provided for the following classification into pragmatic, social, scientific and self-actualization motives, with the most beneficial for the profession motivation - professional and self-actualization motives, while the pragmatic, social and scientific motives may lead to negative outcomes of treatment, due to the specialist’s concentration on external factors, not the treatment itself. The mature medical career choice motives are possible when the person’s “ego” structure is well shaped, with the “real ego” corresponding to the “ideal ego”, which is almost improbable at 17-18years. According to the A. Maslow hierarchy of needs, the career choice from the first, second and third need stages may correspond to the pragmatic, social and scientific motives, disappointment in the career, low medical performance due to their concentration on finances and other factors, not the patient’s benefit, to add to the professional “burnout”. The career choice from the last need stages correspond to the professional motives and personal self-actualization, but, considering the average age of the applicants and financial status of the doctors in Ukraine nowadays, this is unlikely in case of the primary choice. The task of the Education Service Department of a Medical School is detecting motives of a medical student career choice and its gradual correction during the students’ training in a medical school. At the same time, regarding the basic directions of the Healthcare reforming in Ukraine, future possible changes in medical labour financing, providing social protection by the state and state support of the medical career will provide for correction of the career choice, with prevailing social and professional motives instead of the pragmatic ones.

Practice Points.

Motives of the medical career choice are grouped into the pragmatic, social, scientific and professional. The task of the Educational Department of Medical Schools is to detect and correct the prevailing motive groups. The changes of the motives are possible under the performed reforms of Healthcare, which will raise the doctor’s role and protect medical specialists by the State guarantees.

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PHARMACEUTICAL TERMS WITH ONOMASTIC COMPONENT: QUANTITATIVE, STRUCTURAL AND LEXICO-SEMANTIC ANALYSIS

TERMINOLOGIA FARMACEUTYCZNA ZE SKŁADOWĄ ONOMASTYCZNĄ: ANALIZA JAKOŚCIOWA, STRUKTURALNA ORAZ LEKSYKALNO-SEMANTYCZNA

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ABSTRACT

Introduction: The present paper examines the prevalence and role of eponymic terms in the Latin and English pharmaceutical terminologies.

The aim: The authors aim to conduct the quantitative, structural and lexico-semantic analysis of the names of medications with the proprial component.

Materials and methods: The research material in the amount of 147 units was obtained by the continuous sampling from the dictionaries, guidebooks and manuals on prescription-writing using the narrative and component analysis methods, by means of which the arrangement, systematization, classification and interpretation of the structural, semantic and functional features of the units under consideration have been conducted.

Review and conclusions: The research has resulted in the delineation of the following groups of eponymic terms in the pharmaceutical terminologies of Latin and English: (1) semisolid dosage forms (*formae medicamentorum molles*): 81 title (55.1%); (2) liquid dosage forms (*formae medicamentorum fluidae*): 60 lexical units (40.8%); (3) solid dosage forms (*formae medicamentorum solidae*): 6 cases (4.1%). The analysis of 147 units showed that the most extensive group of pharmaceutical terminology units with the eponymic component are the names that specify the dosage form of medication. The prospects for research are in the further in-depth study to examine the tendencies of eponymization in both synchronic and diachronic aspects.

KEY WORDS: medical terminology, pharmaceutical terminology, eponymic terms, terminological collocations, onomastic component

Wiad Lek 2018, 71, 1 cz. II, 217-221

INTRODUCTION

Eponymic terms constitute the most common type of terminological phrases with onomastic component [1, p. 95-98]. A characteristic feature of such nominative units is their branched synonymy. Despite the fact that synonymy is considered to be undesirable for this type of vocabulary, a significant advantage of eponymic terms consists in their conciseness, which predetermines their prevalence in the functional speech [2; 3; 4; 5]. The undeniable advantages of eponymic terms are the lack of polysemy and, in general, their international nature of prevalence and acceptance. The eponymic terms clearly represent the anthropocentric essence of human thinking and language [6], as well as provide the continuity of scientific knowledge.

The analysis of literature on the subject of research has shown that the attention of scientists is focused on the anatomical, histological and clinical terminology, while much less attention is paid to pharmaceutical terminology. The publications of recent years [6; 7; 8; 9], as well as the authors' own researches [10; 11; 12; 13] confirm the fact that eponymic terms (i.e., *nomens* with the proprial component) occupy a significant place in the structure of

medical terminology. It is quite logical that the study of qualitative and quantitative characteristics of eponymic terms that function in different sublanguages does not lose its relevance.

THE AIM

The aim of the research is to conduct the quantitative, structural and lexico-semantic analysis of the names of medications with the proprial component.

MATERIALS AND METHODS

The research material in the amount of 147 units was obtained by the continuous sampling method from the *Extemporaneous Prescriptions for treatment of Skin Diseases* [14], *Prescription-Writing Manual* by V. Yerenkov [15], *Compendium 2010 – Medications* [16], *Latin-Russian Pharmaceutical Dictionary* by T. Kazachenok [17], the two-volume reference book *Medicines* by M. Mashkovskiy [18; 19], the two-volume *Medical Dictionary* by K. Rudzitis [20], *Guidebook of the Extemporaneous Formulations* by

A. Tikhonov [21]. The present paper is largely based on the narrative method of research, by means of which the arrangement, systematization, classification and interpretation of the structural, semantic and functional features of the units under consideration have been conducted. An additional method is the component analysis, used to establish and describe the syntactic structure of pharmaceutical terms with onomastic component.

REVIEW AND DISCUSSION

The analysis of the selected layer of pharmaceutical terms allows us to state that the most numerous group includes the eponymic terms, which specify the pharmaceutical form of medications. From the point of view of syntax, the majority of pharmaceutical eponyms are binomial phrases, formed on the basis of the model which is typical of Latin names with the eponymic component, and can be found in other terminology systems (first of all, anatomical, histological and clinical): noun in Nom. Sing. (rarely – in Nom Plur.) + the surname of the doctor (scientist) in Gen. Sing. That is to say, these terms are formed according to the syntactical non-preposition construction, or “uncoordinated attribute”. At the same time, the noun plays the role of the appellative component, while the eponym acts as the base unit.

Taking into account such characteristics as attribution to dosage forms: **solid** (formae medicamentorum solidae), **semisolid** (formae medicamentorum molles), **liquid** (formae medicamentorum fluidae), – a significant number of terms with the eponymic component is observed among the semisolid dosage forms – 81 lexical unit (55.1%). The largest number of titles (54 cases – 36.8% of the studied units) is represented by ointments (“**unguentum**”), for instance: **unguentum Whitfieldi** (Arthur Whitfield, an English dermatologist, 1868-1947) – *Whitfield’s ointment: contains benzoic acid and salicylic acid (acidum benzoicum et acidum salicylicum)*; **unguentum Credé** (Carl Siegmund Franz Credé, a German gynecologist, 1819-1892) – *Credé’s ointment: contains collargol (Collargolum), distilled water (aqua destillata), lanolin / yellow wax (Lanolinum / cera flava), lard (adeps suillus)*; **unguentum Moro** (Moro Ernest, an Austrian pediatrician, 1874-1951) – *Moro’s ointment, contains 50% of the old tuberculin ointment on lanolin*; **unguentum Hebrae** (Ferdinand Ritter von Hebra, an Austrian dermatologist, 1816-1880) – *Hebra’s ointment is prescribed against scabies (contra scabiem)*; **unguentum Mikulicz-Radecki** (Jan Mikulicz-Radecki, a Polish surgeon, 1850-1905) – *Mikulicz-Radecki ointment contains 1% of silver nitrate and 10% of Peruvian balsam*; **unguentum Listeri** (Joseph Lister, an English surgeon, 1827-1912) – *Lister’s ointment is prescribed as an antiseptic agent*.

In the context of our study, *Averin’s ointment* deserves special attention – **unguentum Averini** (*Averin was a Russian merchant, who lived in St. Petersburg in the 19th century, the exact years of life could not be found*). *Averin’s ointment is used as an antiseptic and anti-inflammatory agent for skin diseases, it is especially effective in the treat-*

ment of scabies (contra scabiem), it is also recommended for the treatment of furunculosis [14]. It should be noted that in 2016, *Averin’s ointment* was included in the list of drugs recommended by the World Organization of Allergists (WAO). In the process of study, we found that in modern dermatology, two versions of *Averin’s ointment* are used, which somewhat differ in composition:

Version 1

Recipe: Hydrargyri amidochloridi 10.0
Adipis suilli depurati 88.0
Olei Bergamiae vel olei Coriandri 2.0
Misce. Da. Signa.

Version 2

Recipe: Hydrargyri amidochloridi 6.0
Adipis suilli depurati 48.0
Olei Lavandulae 1.0
Olei Salviae 1.0
Misce. Da. Signa.

We also consider it necessary to dwell in more detail on such a preparation as *Konkov’s ointment* (**unguentum Concovi**, **unguentum Konkovi** and **unguentum Konsovi**, since there are different Latin spellings of the name “Konkov”), used *ad usum externum* in the treatment of pyoderma, and also as a wound healing agent, for example, for burns and trophic ulcers. Our interest in this preparation is due to the fact that the ointment was at first developed by *Konkov* in two prescriptions, the first one containing such ingredients as ethacridine lactate (*Aethacridini lactas* – 3.0), distilled water (*aqua purificata* – 1.5), honey (*mel apium* – 65.0), vitaminized fish oil (*oleum jecoris Aselli vitaminisatum* – 35.0) and the second, having in its composition 3 dg of ethacridine (*Aethacridini* 0.3), 33.5 grams of fish oil (*olei jecoris Aselli* 33.5), 62 grams of bee honey (*mellis apium* 62.0), 3 grams of birch tar (*Picis liquidae* 3.0), 1.2 grams of distilled water (*Aquae purificatae* 1.2) and currently serves the basis for three types of *Konkov’s ointments* used in dermatology: *Konkov’s ointment with ichthyol* (**unguentum Concovi cum Ichthyolo**), *Konkov’s ointment with benzylpenicillin* (**unguentum Concovi cum Benzylpenicillino**) and *Konkov’s ointment with synthomycin* (**unguentum Concovi cum Synthomycino**).

In the selection process, we detected 1 case of four-component substantive pharmaceutical eponym, which was formed by combining the non-preposition construction with prepositional structure: **unguentum contra coryzam Simanowsky** – *Simanovsky’s ointment against rhinitis* (Nikolay Simanovsky, a Russian otorhinolaryngologist, 1854-1922, a mentee of S. Botkin, the founder of otorhinolaryngology as a separate clinical branch).

As to the dosage form of “**pasta**”, we detected 21 example (14.3%) with eponymic components: **pasta Lassari** (Oskar Lassar, a German dermatologist, 1849-1908) – *Lassar’s paste: contains zinc oxide (Zinci oxydum) and salicylic acid (acidum salicylicum)*; *it is prescribed as a topical protecting and astringent agent*; **pasta Rachmanovi** (O. Rakhmanov, a Soviet neuropathologist, 1878-1948) – *Rakhmanov’s paste and others*.

The dosage form “*linimentum*” is not extensively represented by the eponymic terms: only 6 titles (4% of the studied cases): *linimentum Billrothi* (Christian Albert Theodor Billroth, a German surgeon, 1829-1894) – *Billroth's liniment: contains iodoform (Iodoformium); it is prescribed as an antiseptic; linimentum Vishnevsky (syn. unguentum Vishnevsky)* (Alexander Vishnevsky, a Soviet surgeon, 1874-1948) – *Vishnevsky's balsamic liniment: contains tar (Pix liquida), xeroform (Xeroformium) and castor oil (oleum Ricini); it is intended for treatment of wounds and ulcers; linimentum Rosenthali* (Solomon Rosenthal, a Belarusian and Russian doctor, 1890-1955) – *Rosenthal's liniment: comprises iodine (Iodum), paraffin (Paraffinum), ethyl alcohol (spiritus aethylicus), chloroform (Chloroformium); it is effective for treatment of inflammatory processes.*

The analysis of manual prescriptions of *liquid forms* revealed 60 lexical units, which constitutes 40.8%. In the course of the study, we identified 40 pharmaceutical eponymic terms with the main word “*solutio*”, which is 27.2% of the total number of the examined corpus of terminology units. Hence, in the article on “*Solutio*” (the dictionary by K. Rudzitis [20, p. 509]) there are: *solutio Hayemi* (Georges Hayem, a French physician, 1841-1933) – *Hayem's solution: solution of mercuric dichloride (Hydrargyri dichloridum), sodium chloride (Natrii chloridum) and sodium sulfate (Natrii sulfas); solutio Lugoli* (Jean Georges Antoine Lugol, a French physician, 1786-1851) – *Lugol's solution: water solution of iodine with iodine potassium; solutio Albrighti* (Fuller Albright, an American physician, 1900-1969) – *Albright's solution: solution containing 75.0 of sodium citrate (Natrii citras), 25.0 of potassium citrate (Kalii citras), 140.0 of citric acid (Acidum citricum), 1000 ml of water (Aqua); solutio Burowi* (Karl August von Burow, a German surgeon, 1809-1874) – *Burow's solution: solution of aluminum acetate (solutio Aluminium acetatis); solutio Randalli* (Alexander Randall, an American urologist, 1883-1951) – *Randall's solution: includes acetate, bicarbonate and citrate salts of potassium; solutio Fowleri* (Thomas Fowler, an English doctor, 1736-1801) – *Fowler's solution, which is used for treatment of anemia.*

We identified 3 cases of three-word terminological phrases: *solutio Ringer-Locke* (Sydney Ringer, an English physiologist, 1835-1910; Frank Spiller Locke, an English physiologist, 1871-1949) – *Ringer-Locke solution is prepared ex tempore. The solution contains Natrii chloridi 9.0, Kalii chloridi 2.0, Calcii chloridi 2.0, Natrii hydrocarbonatis 2.0, Glucosi 1.0, aquae pro injectionibus ad 1000 ml.* These terms are based on the scheme: “*solutio*” + the surname of the doctor in Nom. Sing. + “dash” + the surname of the doctor in Nom. Sing. In this context, one can observe the extensive synonymy, for example: *solutio Natrii lactatis composita pro injectionibus, Ringeri lactas, solutio Hartmanni pro injectionibus.*

Noteworthy is the model of eponymic formation where the proprial component – the surname of a doctor or a scientist (physiologist, pharmacologist) ends in a vowel. In these cases, the Latin equivalent preserves the surname in Nominative case. For example: *solutio Magendie* (François

Magendie, a French physiologist, 1783-1855) – *Magendie's solution: contains morphine sulphate; it is prescribed ad usum parenteralem; solutio Tyrode* (Maurice Vejux Tyrode, an American pharmacologist, 1878-1930) – *Tyrode's solution: the modified Locke's solution containing magnesium.*

The word *liquor, oris m* had the following meanings in the classical Latin [20, p. 517]: 1) a liquid state; 2) moisture; 3) sea; 4) transparency. The contemporary anatomical nomenclature uses this term to refer to specific fluids, e.g., *liquor cerebrospinalis* – *cerebrospinal fluid, liquor folliculi* – *follicular fluid, liquor Scarpae syn. endolympha* – *Scarpa s liquor syn. endolympha, liquor amnii* – *amniotic fluid.*

In the pharmaceutical terminology, the aforementioned term refers to a liquid that contains a substance for medical use. The overwhelming majority of them are binomial substantive names (6 cases – 4.1%). For example, *liquor Castellani syn. solutio Castellani* (Aldo Castellani, an Italian physician, 1879-1971) – *Castellani fluid syn. carbol-fuchsin solution; liquor Wickersheimeri* (Jean Wickersheimer, a German anatomist, 1832-1896) – *Wickersheimer's fluid, which is currently used to preserve anatomical preparations and contains arsenic trioxide (Arsenici trioxydum), sodium chloride (Natrii chloridum), sodium sulfate (Natrii sulfas), sodium carbonate (Natrii carbonas), potassium nitrate (Kalii nitris), water (Aqua), ethyl alcohol (spiritus aethylicus), glycerin (Glycerinum).*

It should be noted that in some cases the “*liquor*” component in pharmaceutical terms has the meaning of “*solution*” and is synonymous to the same eponym-less formation with the word “*solutio*”: *solutio Fowleri syn liquor Kalii arsenitis* – *Fowler's solution syn. potassium arsenite solution.*

In the authorized prescriptions of medications, the word “*liquor*” can be used within the meaning of “*rinse*”: *liquor Kartaschowi* – *Kartashov's rinse: contains thymol (Thymolum), menthol (Mentholum) and ethyl alcohol (spiritus aethylicus), as well as the meaning of “formula”:* *liquor Kefferi* – *Keffe's formula* (Haldan Keffer Hartline, an American physiologist and biophysicist, 1903-1983).

The conducted research confirmed that pharmaceutical terminology, as other terminology sublanguages of medicine, often contains the equivalents of eponyms – the multiple-word descriptive terms such as: *solutio Locke-Ringeri syn. solutio Natrii chloridi composita* – *Ringer-Locke solution syn. composite solution of sodium chloride; solutio Burowi syn. solutio topicalis Aluminium acetatis* – *Burow's solution syn. topical solution of aluminum acetate; liquor Burowi syn. liquor Aluminium subacetatis* – *Burow's fluid syn. solution of basic aluminum acetate.* Analyzing this phenomenon, we came to the conclusion that eponyms are more concise and space-saving, and thus more convenient for use than the corresponding multiple-word descriptive terms.

While examining such liquid dosage form as “*mixtura*” (mixture), we found 8 eponyms (5.4%): *mixtura Bechterevi* (Vladimir Bekhterev, a Russian neuropsychiatrist, 1857-1927) – *Bekhterev's mixture is used for treatment of heart diseases; a combined preparation, containing infusion of the spring adonis grass (infusum herbae Adonidis vernalis ex 6.0 – 180 ml), sodium bromide (Natrii bromidum 6.0), codeine phosphate*

(Codeini phosphas 0.2); *mixtura Tellysniczky* (K. Tellysniczky, a Hungarian anatomist, 1868-1932) – *Tellysniczky's mixture: a fixative solution containing potassium bichromate (Kalii bichromas), water (Aqua) and the so-called glacial acetic acid (Acidum aceticum anhydricum syn. Acidum aceticum concentratum), that is, acetic acid whose concentration is approaching 100%*; *mixtura Ringeri* – *Ringer's mixture: a sterile solution containing 900 mg of sodium chloride (Natrii chloridum), 35 mg of potassium chloride (Kalii chloridum), 36 mg of calcium chloride (Calcii chloridum); it is prescribed as a physiological saline for topical application*; *mixtura Krasnogorsky* (Mykola Krasnogorsky, a Soviet pediatrician and physiologist, 1882-1961) – *Krasnogorsky's mixture*; *mixtura Seppi* (Yevgeniy Sepp, a Russian neuropathologist, 1878-1957) – *Sepp's mixture*, *mixtura Pavlovi* (Ivan Pavlov, a Russian physiologist, 1849-1936) – *Pavlov's mixture*.

The medicinal form of “*lotiōnes*” denotes the official liquid preparations for application to the skin, washing eyes, ears, larynx and nose. We found one example with the eponymic component (0.7%): *lotio Goulardi* (Thomas Goulard, a French physician, 1697-1784) – *Goulard's lotion (also known as Goulard's water), which is a diluted solution of basic lead acetate (Solutio Plumbi subacetatis diluta)*.

We found 4 (2.7%) eponymic terms with the dosage form *balsamum, i n* – *balsam*, which is a liquid with aromatic odor, e.g., *balsamum Schostakowsky* (Mikhail Shostakovskiy, a Russian organic chemist, 1905-1983) – *Schostakowsky balsam: promotes the wound cleansing and development of granulation*.

We found 1 (0.7%) eponymic terms with the dosage form *spiritus Mikulitschi* (*Mikulicz's spirit*), which is intended for treatment of furunculosis and is composed of [14]: *oleum Olivarum* – 12.0, *solutio Kalii hydroxydi vel solutio Natrii hydroxydi* – 14 ml, *spiritus aethylicus* – 60 ml, *aqua purificata* – 34 ml).

Formae medicamentōrum solidae with the eponymic component are the rarest: we detected only 6 examples (4.1%) of “*pulvĕres*”, e.g., *pulvis Kontschalowsky* (Maksim Konchalovsky, a Soviet physician, 1875-1942) – *Konchalovsky's powders*; *pulvis Botkini* (Sergey Botkin, a Russian physician, 1832-1889) – *Botkin's powder: effervescent powder containing sodium bicarbonate (Natrii bicarbonas), tartaric acid (acidum tartaricum) and sodium sulphate (Natrii sulfas); it is prescribed as a laxative*; *pulvis Doveri* syn. *pulvis Ipecacuanhae opiatus, Pulvis Opii et Ipecacuanhae compositus* (Thomas Dover, an English doctor, 1660-1742) – *Dover's powder: contains opium and ipecacuanha; it is prescribed against cough*; *pulvis Preobragensky* (Boris Preobrazhenskiy, a Soviet otolaryngologist, 1892-1970) – *Preobrazhenskiy's powder: contains white streptocide (Streptocidum album), Sulfazolium, Sulfidinum*; *pulvis Rosentuli* (M.A. Rosentul, a Russian dermatovenereologist, 1892-1981) – *Rosentul's powder is used for treatment of certain skin diseases*, *pulvis Worobjevi* (Andrey Vorobyov, a Russian hematologist, 1928) – *Vorobyov's powder is prescribed for treatment of epilepsy*.

Furthermore, we conducted the research as to the presence of the same eponymic name as a component of different dosage forms: *solutio physiologica Ringer-Locke*

and *tabulettae Ringer-Locke; unguentum Wischnewsky, linimentum Wischnewsky* and *liquor Wischnewsky, spiritus Mikuliczi (Mikulitschi)* and *unguentum Mikuliczi (Mikulitschi)*. In our opinion, this fact testifies to the competence of the authors, the evolution of the research thinking and professional experience. In addition, it should be noted that one can observe the same surnames in the list of clinical terms with the eponymic component. For example, in the *Latin-Ukrainian Dictionary of Clinical Terms* [10], the following names are recorded: *Mikuliczi syndromum* and *Mikuliczi morbus, Behtererevi morbus, Hebra-Kaposi impetigo herpetiformis*.

Summarizing the aforesaid, it should be noted that for the formation of eponymic names in the pharmaceutical terminology, the following model is the most productive: the signifying word in Nom. Sing. + eponym in Gen. Sing. The typical structural formula consists of two components. The synonymic rows are rarely observed.

The absence in the studied lexicographic sources of any examples with the eponymic component for other known dosage forms, e.g., *tinctura, extractum, sirupus, suspensio, suppositorium*, requires further in-depth study in order to follow the trends of eponymization in both synchronic and diachronic aspects.

CONCLUSIONS

The results of the study confirmed the fact that the pharmaceutical terminology contains much less eponymic names than other sublanguages of medicine. The analysis of 147 units showed that the most extensive group of pharmaceutical terminology units with the eponymic component are the names that specify the dosage form of medication. In the overwhelming majority, they are binomial terminological phrases formed on the basis of the model which is typical of Latin names with the eponymic component and are found in other terminology systems (first of all, anatomical, histological and clinical): noun in Nom. Sing. (much less often – in Nom Plur.) + the surname of the inventor in Gen. Sing. At the same time, the noun plays the role of the appellative component, while the eponym acts as the base unit. Syntactically, such terms belong to the “uncoordinated attribute” group.

The prospects for further research are in the study of pharmaceutical terms with other onomastic categories, in particular, the toponymic components, as well as eponymic terms with the abbreviated version of the inventor's surname.

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Received: 02.10.2017

Accepted: 11.01.2018

INFLUENCE OF RISK FACTORS ON DEVELOPMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND LEGISLATIVE FOUNDATIONS FOR COPD MEDICAL CARE IN UKRAINE

WPŁYW CZYNNIKÓW RYZYKA NA ROZWÓJ PRZEWLEKŁEJ OBTURACYJNEJ CHOROBY PŁUC ORAZ PODSTAWY PRAWNE OPIEKI ZDROWOTNEJ NAD PACJENTAMI Z POCHP NA UKRAINIE

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ABSTRACT

Introduction: Out of all respiratory diseases COPD is the leading cause of death and is characterized with diffuse non-reversible airway obstruction. Many various components play role in development and progression of this disease, while COPD risk factors play the most prominent role. Further progress in healthcare system development around COPD in Ukraine requires analysis of legislation, regulating pulmonological medical service in Ukraine.

The aim: To analyze the influence of major risk factors on the development of chronic obstructive pulmonary disease and to determine key legislative aspects of the organization of medical care for COPD patients in Ukraine.

Materials and methods: 50 medical literature sources were systematically reviewed as the material for the research of COPD risk factors and their impact on studies disease. Also, an analysis of existing legislative acts regulating the pulmonological medical care in Ukraine, specifically, in patients with COPD, was conducted.

Conclusions: There is a need to develop and implement a set of organizational and medical measures aiming at addressing the priorities of public healthcare, and specifically improvement of the quality of medical care for patients with chronic obstructive pulmonary disease in Ukraine.

KEY WORDS: chronic obstructive pulmonary disease, risk factors for COPD, legislation on COPD management, Ukraine

Wiad Lek 2018, 71, 1 cz. II, 222-225

INTRODUCTION

Respiratory diseases still hold their leading position among all diseases globally with regards to burden. Chronic obstructive pulmonary disease (COPD) has a notable special place among those, since presenting a major medical and scientific problem to public communities.

Out of all respiratory diseases COPD is the leading cause of death and is characterized with diffuse non-reversible airway obstruction. COPD and bronchial asthma contribute to 4 million deaths annually, which is three times more than deaths from diabetes mellitus [1].

Modern science describes COPD as a disease with multifactorial etiology. Many various components play role in development and progression of this disease, while COPD risk factors play the most prominent role.

There is a consensus around key risk factors in the onset of the COPD: tobacco smoking, industrial and household pollution, dust and chemical agents from wood fire, and infectious diseases [2, 3, 4, 5].

Incidence of COPD has increased threefold during the last decade, mainly driven by air pollution, spread of tobacco smoking, and population ageing [3, 4].

Tobacco smoking is most frequent etiological factor of COPD [1, 3, 5]. Latest 2018 Global Initiative for Obstructive Lung Disease (GOLD) report emphasize cigarette smoking as the most well studied COPD risk factor [2].

Some studies shown 6 million deaths occur due to tobacco smoking, and more than 600 thousand die from passive smoking, which makes decrease of the disease incidence inevitably growing. 58% of young men in Ukraine are smokers, with around 46.8% of whom are adolescents of 13-16 years of age (this is the largest proportion among 26 European countries) [1].

THE AIM

The aim of this paper is to analyze influence of key factors of chronic obstructive pulmonary disease development and progression and to evaluate major legislative aspects of COPD medical care in Ukraine.

MATERIALS AND METHODS

Material for the research of risk factors of COPD were data from more than 50 scientific papers, which describe

various factors of chronic obstructive pulmonary disease development. Analysis of current legislation regulating pulmonology medical care in Ukraine, particularly for COPD patients.

REVIEW AND DISCUSSION

To date there is a large body of scientific knowledge around inhaled industrial/occupational and domestic air pollution, which both play a sizable role in development of COPD. There is a wide spectrum of professions, largely exposed to harmful occupational factors (miners, casters, grinders, electric welders, textile, agriculture, and tobacco production workers etc.).

In NHANESIII (USA) study which included 10 000 adults aged from 30 to 75 years, the prevalence of COPD developed from occupational risk factors was estimated as 19.2%, population of never smokers demonstrated prevalence of COPD of 31.1%. The paper emphasizes the impact of organic and non-organic dust, chemical agents and gases was clearly underestimated from COPD development risk perspective [1].

In fact, one the first reports, recognizing professional risk factors in development of COPD (toxic and irritating substances, biofuel combustion products, gases, smoke, dust of biological origin) started to be included into GOLD 2012 [6].

Though still the major risk factor for COPD is tobacco smoking. This risk factor alone per some authors may contribute to 80% of all COPD cases. And there is a disturbing evidence, demonstrating there is an anticipated growth of smokers cohort to more than 3 billion people globally by 2030 [7].

Some researchers demonstrated low birth weight and individual airway hyperreactivity play role in development of COPD [5, 8].

Some diseases, like tuberculosis and HIV-infection, could also impact development of emphysema in smokers, conditioning other comorbidities as respiratory tract infections and bronchial asthma [6].

Misdiagnosis of COPD as bronchial asthma (BA) can also widely occur since differential diagnosis is complicated with inflammatory nature of both diseases, affecting small airways and characterized by airflow limitation with close medicinal treatment options. Despite these similarities, these two conditions represent two independent broncho-obstructive diseases with different pathogenesis, and thus different medical management.

BA and COPD are characterized with different etiological factors. While BA has atopy, genetic factors, causing atopic diseases among family members, COPD is mainly (90% of instances) caused by either tobacco smoking or professional harmful factors exposure [6].

Comorbidities in COPD further contribute to rapid progression of the disease and worsen prognosis and quality of life in affected patients. Wide range of comorbidities is reported in 80% of COPD cases. Around half of patients with COPD have 4 comorbidities and more [1].

Retrospective analysis of patient medical records in COPD elderly population, conducted by Stupnytska G., has shown arterial hypertension (64,7%), diabetes mellitus (28,5%), obesity (22,4%), ischemic heart disease (19,9%), arrhythmia (16,6%), congestive heart failure (13,8%) as the most frequent comorbidities in this study population [8].

Some authors believe genetic factors play an important role in COPD onset [6]. According to the research data, association exists between some specific genes (for example α -1-antitrypsin deficiency) and development of COPD, though prevalence of these genetic factors is relatively low in general population.

In general, there are two major groups of development factors of chronic obstructive pulmonary disease: external and internal.

External factors include:

1. Long-term tobacco smoking (smoking index – 10-20 pack years), passive tobacco smoking.
2. Industrial (occupational) and indoor air pollution (pollutants, coal, dust, cadmium, gases and fumes from chemical substances, biomass fuel combustion products used for heating and cooking).
3. Infections (severe infections in children, respiratory infections, HIV).
4. Deficient socio-economic conditions (limited access or restrictions to healthy food, overpopulation, hypothermia, pernicious habits)

Internal risk factors include:

1. Genetic factors (inherited α -1-antitrypsin deficiency).
2. Bronchial hyperreactivity (associated with long-term exposure to tobacco smoking, concomitant bronchial asthma).
3. Incomplete lung development (complications associated with pregnancy, harmful conditions in childhood).

Discussion around healthcare system development around chronic obstructive pulmonary disease in Ukraine is not practical without analysis of legislative norms around this subject matter. Careful review of key aspects of various legislative acts, regulating pulmonological medical service in Ukraine, is required for this purpose.

Major legislative norm describing public relations around healthcare is the Law of Ukraine dated 19.11.1992 #2801-XII “Fundamental Legislation of Ukraine on Healthcare”. This law is based on the Constitution of Ukraine and provides every person with guarantees around natural, inalienable, and immutable rights for healthcare.

The Order of the President of Ukraine dated 07.12.2000 affirmed the “Concept of Ukrainian Population Healthcare Development”, which aimed to ensure provision of affordable, qualified medical care to every citizen of Ukraine. Pursuant to this Order Ministry of Health of Ukraine issued the order dated 28.10.2003 #499 “On Approval of Instructions for Medical Care to Patients with Tuberculosis and Non-specific Pulmonary Diseases”, which established the instructions on diagnostics, clinical classification, and medical management of chronic obstructive pulmonary disease.

According to the Law of Ukraine dated 05.10.2000 #2017-III “On the State Social Standards and the State Social

Guarantees” the anticipated unification of quantitative and qualitative requirements to medical care in medical institutions in Ukraine was matched with the development of the Order of the Ministry of Health of Ukraine dated 10.01.2005 #7 “On Approval of Standards of Provision of Medical Care for Specialty “Occupational Pathology” in Outpatient Clinical Institutions”. This order was introducing the standards of medical care to patients with chronic obstructive pulmonary disease or occupational etiology (occupational dust, chemical substances, gases, fumes, and vapors).

Medical care in patients with respiratory tract diseases, particularly with chronic obstructive pulmonary disease, still required further improvement though. Cross-collaborative research among pulmonology experts in Ukraine, lasting from 2005 to 2007, resulted in development of the first modern treatment protocols on the management of pulmonary tract diseases. These protocols were established with two Orders of the Ministry of Health of Ukraine – one dated 03.07.2006 #433 “On Approval of Protocols on Provision of Medical Care for Specialty “Pulmonology” [9] and the second dated 19.03.2007 #128 “On Approval of Clinical Protocols on Provision of Medical Care for Specialty “Pulmonology” [10].

The Cabinet of Ministers of Ukraine passed the Resolution dated 17.02.2010 #208 “Some Questions on Improvement of Healthcare System”, which was followed by development of “Unified Clinical Protocol of Primary, Secondary (Specialized), Tertiary (Highly Specialized) Medical Care and Medical Rehabilitation “Chronic Obstructive Pulmonary Disease”. Experts in pulmonology along with other associated specialties professionals and academic institutions collaborated closely with the Ministry of Health of Ukraine to contribute to this detailed clinical protocol, having reviewed and included key aspects from adapted clinical guideline “Chronic Obstructive Pulmonary Disease” as the major source of evidence-based information on management of COPD. The clinical protocol was approved with the Order of the Ministry of Health of Ukraine dated 27.06.2013 #555 “On Approval and Implementation of Medical and Technical Documents on Standardization of Medical Care for Chronic Obstructive Pulmonary Disease” and is now the key regulation around medical care for patients, suffering from COPD [11].

Since public health preservation is the strategic mission of any state globally, Ukraine boldly positions its strategy around further potential in development of pulmonological service, given a high incidence and prevalence of COPD in Ukrainian population. Main priorities in the COPD management healthcare strategy in Ukraine include disease prevention and further advances in quality of COPD medical care.

CONCLUSIONS

Chronic Obstructive Pulmonary Disease progressively has been showing signs of the most serious developing world healthcare issue. Key risk factors for COPD are well

established and include tobacco smoking, occupational and indoor air pollution, respiratory infections, inherited or congenital factors, and deficient socio-economic conditions. Frequency and severity of comorbidities (hypertonic disease, diabetes mellitus, cardio-vascular diseases, blood lipid disorders, depression, osteoporosis, tuberculosis, pneumonia) largely impact quality of life and mortality in patients with COPD.

Identification of chronic obstructive pulmonary disease risk factors and their weight in specific populations of interest is an important aspect for further defining the advanced medico-social model of medical care in COPD.

Ukraine has made a notable step in development of relevant and necessary legislation around pulmonology healthcare public service over the last decade, primarily focusing on treatment and rehabilitation of affected population cohort. At the same time, there is a tangible gap in legislative norms aiming at improving specifically the organization of medical care for patients with COPD, which could largely contribute for the benefit of ongoing medical reform in Ukraine.

Further research perspectives exist around development and implementation of complex organizational and medical measures, focusing on priority areas of the state healthcare system, including improving quality and accessibility of medical care for patients with chronic obstructive pulmonary disease.

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This work is a part of the authors contribution to the research, conducted at the Shupyk National Medical Academy of Postgraduate Education – “Substantiation of healthcare subsystem management models and strengthening of public health in Ukraine in accordance with the European strategies” (2014-2019, State Registration Number 0115U002160).

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Received: 23.10.2017

Accepted: 01.02.2018

ENSURING RIGHT TO ORGANIC FOOD IN PUBLIC HEALTH SYSTEM

ZAPEWNIENIE PRAWA DO ŻYWNOŚCI ORGANICZNEJ W PUBLICZNYM SYSTEMIE OCHRONY ZDROWIA

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ABSTRACT

Introduction: Human health directly depends on safety and quality of food. In turn, quality and safety of food directly depend on its production conditions and methods. There are two main food production methods: traditional and organic. Organic food production is considered safer and more beneficial for human health.

Aim: to determine whether the organic food production method affects human health.

Materials and methods: international acts, data of international organizations and conclusions of scientists have been examined and used in the study. The article also summarizes information from scientific journals and monographs from a medical and legal point of view with scientific methods. This article is based on dialectical, comparative, analytic, synthetic and comprehensive research methods. The problems of effects of food production methods and conditions on human health have been analyzed within the framework of the system approach.

Conclusions: Food production methods and conditions ultimately affect the state and level of human health. The organic method of production activity has a positive effect on human health.

KEY WORDS: organic farming, environment, organic food, human health

Wiad Lek 2018, 71, 1 cz. II, 226-229

INTRODUCTION

Among other things [1], human health depends on food production conditions and methods. It is believed that people receive various chronic diseases and eventually their health deteriorates, quality of their life decreases due to consumption of food containing various dangerous compounds (nitrates, heavy metals, residues of pesticides, herbicides and other substances of chemical synthesis, etc.) used in traditional production methods. Introduction of the organic production method is a guarantee not only for health of a person consuming given products, but also for health of a person directly involved in food production. Moreover, with organic production methods, the environment is not subjected to damaging effects. But so far, organic production methods are rather an exception to the rules than a rule. The regions with the largest areas of organically managed agricultural land are Oceania (22.8 million hectares or 45 percent of the global organic farmland), Europe (12.7 million hectares or 25 percent of the global organic farmland) and Latin America (6.8 million hectares or 15 percent). The countries with the most organic agricultural land are Australia (22.7 million hectares), Argentina (3.1 million hectares) and the United States (2.0 million hectares) [2].

THE AIM

To determine whether the organic production method of food affects human health.

MATERIALS AND METHODS

The development of organic production is a political objective of the EU. The main European documents intended to regulate organic production include Council Regulation (EC) No 834/2007 of 28 June 2007 on organic production and labelling of organic products, repealing Regulation (EEC) No 2092/91 and revising the basic requirements for organic production and labelling of organics; setting out the principles, aims and overarching rules of organic production and defining how organic products were to be labelled more clearly. The regulation set a new course for developing organic farming further, with the following aims: sustainable cultivation systems a variety of high-quality products, greater emphasis on environmental protection, more attention to biodiversity higher standards of animal protection, protecting consumer interests. In organic farming, closed cycles using internal resources and inputs are preferred to open cycles based on external resources. If the latter are used, they should be organic materials from other organic farms natural substances materials obtained naturally, or mineral fertilisers with low solubility. Exceptionally, however, synthetic resources and inputs may be permissible if there are no suitable alternatives. Such products, which must be scrutinised by the Commission and EU countries before authorisation, are listed in the annexes to the implementing regulation (Commission Regulation (EC) No. 889/2008) [3]. Art.

34 of the above-mentioned Regulation prescribes special rules for the marketing of products produced in third countries. Moreover, the detailed rules for organizing the procedure for imports of organic products from third countries were separately set out in Council Regulation (EC) No. 1235/2008 of 8 December 2008. In addition to this from 27 January 2009 Commission regulation (EC) № 152/2009 laying down methods of sampling and analysis for the official control of feed. Selection of specimens for official forage control to determine components, additives and undesirable substances, with the exception of residues of pesticides and microorganisms, is carried out in accordance with the methods set out in Annex I to this Regulation. Since the export-import of organic products always has the risk of finding residues of prohibited pesticide substances, in December 2015, the European Commission proclaimed more stringent Guidelines on additional official controls on organic products imported from Ukraine, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Uzbekistan and the Russian Federation. On November 29, 2016, the Commission revised but did not amend the Guidelines for Ukraine, the Russian Federation and Kazakhstan, which came into force on January 01, 2017.

Another common way to regulate carrying out organic production around the world is implementation of integrated Organic Farming Programmes, which should combine the entire system of the taken legal and organizational measures into a single strategy, arranging general condition for development of organic agriculture in the state. For example, in most European countries, similar programs were introduced in the 1990s: in Norway - in 1995, in Finland, the Netherlands and Sweden - in 1996, in France - in 1997, in the USA - in 1999 [4].

Many countries around the world have relevant legislation, for instance, in Poland there is current Act of Poland on Organic Farming of 25 June 2009, in Sweden - Act of Sweden on Organic Production Control of 23 May 2013, in Germany - Ecological Production Act Implementation Ordinance of 11 January 2010 and Eco Labelling Act of 10 December 2001, in Slovenia - Regulation on Organic Production and Processing of Agricultural Products and Foodstuffs of 13 July 2010, in Ukraine – the Law of Ukraine of 03 September 2013 No. 425 ‘On Production and Trade of Organic Agricultural Products and Raw Materials’, in Kazakhstan – the Law of the Republic of Kazakhstan of 27 November, 2015 No. 423-V ‘On Production of Organic Products’ and others.

And some countries include certain provisions on organic production into the legislation regarding environmentally friendly agriculture. The Czech Republic can be an example of the latter since the ecological agriculture is specifically distinguished and regulated by law - The Czech Act on Ecological Agriculture No. 242/200. We can also give examples of the Croatian Act on Ecological Production and Labeling of Eco-products No. 139/2010, the Law of the Republic of Azerbaijan of 13 June, 2008 No. 650 ‘On Environmentally Friendly Agriculture’ which regulates re-

lations concerning production, processing and trade of the environmentally friendly agricultural and food products ensuring health and safety of the public, land, water, plants and animals of the Republic of Azerbaijan. The notion of ‘environmentally friendly’ used in this law has the same meaning as ‘biological’, ‘organic’ and ‘natural’ concepts used in international law. There is a similar approach to the legislation on organic products in the Republic of Moldova, in particular, in the Law of the Republic of Moldova of 9 June, 2005 No. 115-XVI ‘On Environmental Agricultural Production’.

Despite the fact that in many countries, the demand for organic products is growing rapidly, there is a debate of long duration in scientific circles whether organic production methods lead to improvement of food quality and safety, as well as to improvement and stability of human health or not. The demand for organic products is largely driven by consumer perceptions that organic farming is more sustainable, which means that quality and safety of organic food are higher in comparison with food produced with traditional, intensive farming. One more argument for organic production is the need for solving environmental problems, ensuring biodiversity and public health. At the same time, it is important for agricultural producers to develop organic production to increase competitiveness in the world markets. But not as actively as the positive characteristics, all over the world, they also discuss negative features of organics: researches have shown that on average yields in organic farming are 20-25% lower than in traditional one. Agricultural producers need more land to grow a similar volume of crops, and additional land development for agriculture is a major factor in reducing a range of wildlife and negative climate changes.

Thus, the basis of human health is proper nutrition. Development and constant renewal of cells and tissues of the body is provided exactly by food which is a source of energy that is so necessary for the human body. So, there is indisputable connection of nutrition and human health.

REVIEW AND DISCUSSION

In scientific circles, there are three main views on the impact of organic products on human health. Such views are based on comparison of usefulness of crops, not only when the growing system is the sole difference, but also taking into account the variety of places of their cultivation, soil quality, irrigation methods, plant varieties, conditions of harvesting, storage methods, etc. [5, 6]. Let us examine them:

1. Organically grown products have a totally beneficial effect on human health.

Proponents of this approach place high standards of organic products quality, absence of harmful impurities, pathogens, parasites, allergenic components, genetically modified organisms and substances made on their basis among the benefits of using organic products for human health. Another advantage of organic products is maintaining nutritional properties, quality, safety and natural

composition while processing them, since only natural processing methods and traditional recipes, natural substances and packaging materials are used [7]. Organic food production is also safe for the environment, which ultimately has a positive effect on human health.

Moreover, results from a small number of human cohort studies indicate that there are positive associations between organic food consumption and reduced risk/incidence of certain acute diseases (e.g. pre-eclampsia, hypospadias) and obesity [8].

British scientists have carried out a series of studies which show emotional effects caused by organic food. In terms of emotions, organics is perceived as more healthy, since firstly, it is more expensive, and secondly, it is grown with minimal use of chemicals. Some non-organic products have been labelled as 'organic', and their taste has been perceived by respondents as 'organic' [9]. So, even positive emotional effect while eating organic food can be considered beneficial for human health.

However, using organic methods in agriculture is still considered to be the main arguments for health utility of organic products, as the main idea of organic food production is avoidance of all non-organic farming methods which means that the use of pesticides, artificial fertilizers, antibiotics, growth hormones and similar things is strictly forbidden. Instead, organic food producers use all natural farming methods such as crop rotation, composting, companion planting, stimulating biodiversity, etc. As a result, organic products pose no risk of pesticide residues nor presence of other potentially harmful chemicals. Although conventionally grown food is claimed to be safe, absence of all non-natural ingredients makes organic food without a doubt a healthier and safer choice because the long term effects of those "safe" doses of pesticides, preservatives and other chemicals remain unknown. They may be harmless but they may be also seriously harmful [10]. It has been shown that pesticide residues in food can promote cancer, Parkinson's disease and endocrine abnormalities [11,12].

Some studies have shown that the level of nutrition and content of vitamins (especially vitamin C), as well as some minerals and polyphenols - natural antioxidants that help strengthen the human immune system - are higher in crops grown with organic farming methods. The researchers argue that organic products have a higher level of phosphorus, zinc, magnesium, vitamin C, calcium, potassium, and iron. This difference is particularly noticeable in products of animal origin: meat, eggs, dairy products [13].

2. Organically grown products adversely affect human health.

There is growing popularity of the movement of opponents of organic production all over the world. They are rather skeptical about usefulness and safety of organic products. Thus, Alex Avery argues that the future belongs to biotechnologies which should be used instead of the current organic method of production activity. He emphasizes that many studies show that so-called organic products, firstly, contain more harmful substances, and secondly, it is their cultivation that causes great harm to the nature.

The author believes that the thing is that a rather limited amount of fertilizers, pesticides, herbicides etc. are used organic farming. Most of them are completely ineffective. For example, organic farms use copper sulfate rather actively as it is practically the only pesticide permissible in organic farming. But it is extremely toxic. It is three times more toxic than 'non-organic' captan or pyraclostrobin used at traditional farms [14]. Moreover, organic farms use highly toxic pyrethrin and sulfur, spraying plants with technical oils to fight insects. Since all these substances are less effective than modern chemicals, they are used in the organic farming more often than ordinary pesticides, herbicides and insecticides, and in large quantities [14].

3. Nutritional properties of products grown with organic methods do not differ from those of products grown in the traditional way.

Having conducted researches in the field of nutrition, some British scientists did not reveal any significant differences in the content of nutrients in organic food and products grown with traditional farming. In most comparative analyses, a significantly higher concentration of vitamins, minerals, or other useful trace elements in organics, as a rule, were not detected. Minor differences were registered only in three indices: organic food has a higher content of nitrogen, but less phosphorus and acidity [9]. That is, organic food does not differ from the usual products in terms of health benefits [15].

Consequently, the results of comparison of contents of organic and traditionally grown crops may be different, namely: they can show that there are more nutrients for human health in organic crops [16]. However, sometimes the results of studies are opposite [17], or the results of studies indicate that there is no particular difference between the two methods of cultivating agricultural products [18].

Some authors believe that other factors, namely a type of plants, year, place, environment, genotype selection, cultivating place, weather and time of harvesting, etc., are more important for a positive impact on human health than an organic or traditional way of cultivating agricultural products [19].

There are no definitive and universally recognized scientific research results to compare positive or negative effects of traditional or organic farming products on the human body. It is therefore currently not possible to quantify to what extent organic food consumption may affect human health.

CONCLUSION

It is difficult enough to become a proponent of one or another theory, given the complexity of conducting specific research as to an effect or absence of an effect of organic products on the human body and human health. In order to measure healthiness, one would need to have a group of humans eating only organic and another one eating only conventional food, and then after a while compare which group is healthier [20]. But taking into account all the effects, methods and conditions of production activity

aimed at organic food products in the aggregate, it can be concluded that the organic method of production activity has a positive impact on the state and level of human health.

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Received: 08.10.2017

Accepted: 18.02.2018

CECHY OSOBOWOŚCI SPRAWCÓW RÓŻNYCH TYPÓW PRZESTĘPSTW

PERSONALITY TRAITS OF PERPETRATORS OF VARIOUS TYPES OF CRIMES

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¹ KOŁO NAUKOWE PRZY ODDZIALE KLINICZNYM CHORÓB SERCA I NACZYŃ Z PODODDZIAŁEM INTENSYWNEGO NADZORU KARDIOLOGICZNEGO KRAKOWSKIEGO SZPITALA SPECJALISTYCZNEGO IM. JANA PAWŁA II, INSTYTUT KARDIOLOGII COLLEGIUM MEDICUM UNIwersYTETU Jagiellońskiego, KRAKÓW, POLSKA

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STRESZCZENIE

Praca przedstawia projekt badawczy zrealizowany w Zakładzie Karnym w Nowym Wiśniczu z udziałem skazanych za: morderstwa, przestępstwa na tle seksualnym, kradzieże i rozboje, załaganie z alimentami oraz znęcanie się nad bliskimi. Badania przeprowadzono za pomocą polskiej adaptacji testu PAI dokonanej przez autorów pracy. Prezentowane wyniki i ich statystyczne analizy ukazały specyficzne cechy osobowości sprawców poszczególnych grup przestępstw. Rezultaty badań mogą być wykorzystane w resocjalizacji osób zaburzonych, uzależnionych, a także stanowić podstawę do opracowania programu działań zapobiegających przestępczości.

SŁOWA KLUCZOWE: przestępczość więźniów, osobowość, morderstwo, znęcanie się, alimenty, wykorzystywanie seksualne, kradzież

ABSTRACT

This study was conducted in Nowy Wiśnicz, with prisoners sentenced for: murders, sex crimes, theft and robbery, maintenance, bullying. A Polish adaptation of PAI test, made by the author of the study, was used. The study results and its statistical analysis showed characteristic personality features of particular criminal groups can be used in rehabilitation of disturbed people, addicts, and become the basis for preparing actions reducing frequency of committing crimes.

KEY WORDS: criminality, personality, prisoners, murder, bulling, maintenance, sexual abuse, theft

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WSTĘP

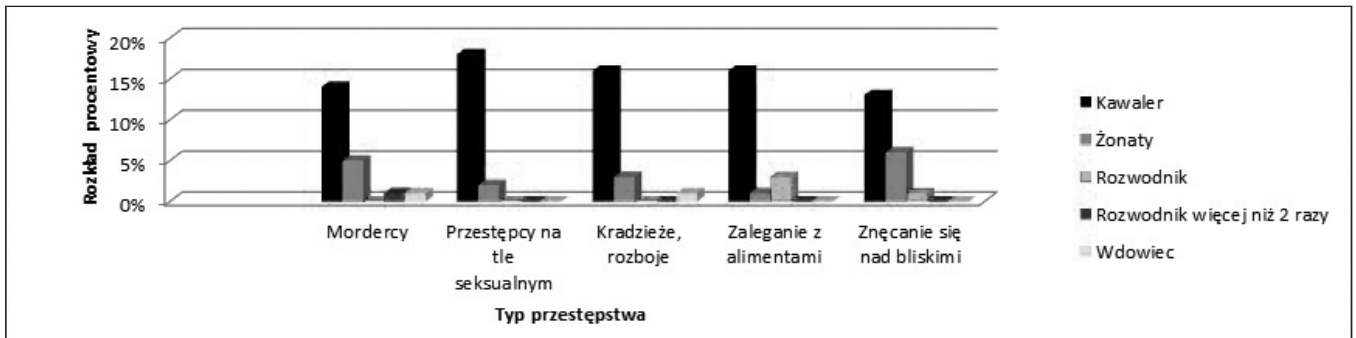
Zachowania przestępcze można zaobserwować w codziennym życiu. Ich świadkami możemy być czy to będąc bezpośrednimi obserwatorami, czy też poprzez mass media lub portale społecznościowe. Z problemem działań przestępczych ludzkość zmagą się od wielu wieków. Każda nauka, religia, podejmuje rozważania na temat czynów złych i dobrych. Natura ludzka jest odmienna od natury pozostałych organizmów żywych. Człowiek jest obdarzony rozumem i wolną wolą. Jest zarówno dobry, jak i zły. Predyspozycje do bycia dobrym są wrodzone. W ciągu życia mogą one na skutek chorób, w tym psychicznych, oraz wpływów środowiskowych, ulec przekształceniu, powodując utratę zdolności do rozpoznawania swoich czynów. Trudno ocenić, czy zachowania patologiczne są uwarunkowane genetycznie, czy też są efektem urazów, chorób lub wpływu środowiska [1–4].

Główne cechy osobowości sprawców zabójstw to: egocentryzm, niewykształcona osobowość wyższa, nieprzystosowanie społeczne i niewykształcone postawy moralne, niski poziom świadomości społecznej, agresja, infantylizm. Przestępców na tle seksualnym cechuje: wrogość, egocentryzm, dominacja, nieumiejętność tworzenia

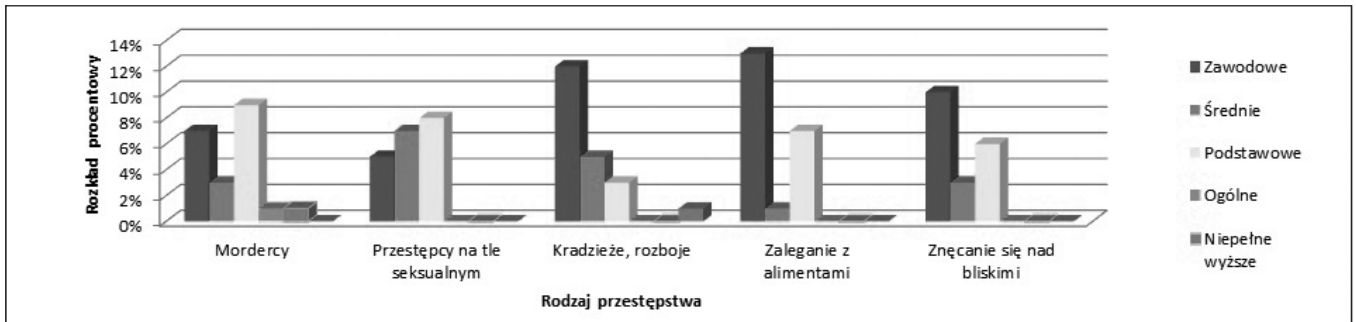
satysfakcjonujących związków międzyludzkich. Zabójcy na tle ekonomicznym są lekkomyślni, nie mają zbyt wielu pozytywnych kontaktów z ludźmi. Powyższe wymienione cechy różnią się ilościowo, oraz natężeniem w zależności od popełnionego przestępstwa [4].

Zaburzenia osobowości występują dosyć często, niekiedy stwierdzone są w warunkach poradni czy oddziałów psychiatrycznych, a niekiedy dopiero w momencie popełnienia przestępstwa. W konflikt z prawem popadają najczęściej osobnicy z antyspołecznym zaburzeniem osobowości. Stanowią około 3% populacji z tego 4/5 to mężczyźni, a jedynie 1/5 kobiety. Antyspołeczne zaburzenie osobowości można częściej spotkać wśród więźniów, albowiem wśród nich takich jednostek jest od 20% do 70%. Są oni niewrażliwi na prawa drugiego człowieka, zachowują się agresywnie, kłamią, kradną, oszukują, podejmują działania destrukcyjne, nie potrafią się adaptować, tworzyć trwałych związków, często bywają uzależnieni od alkoholu, narkotyków [1].

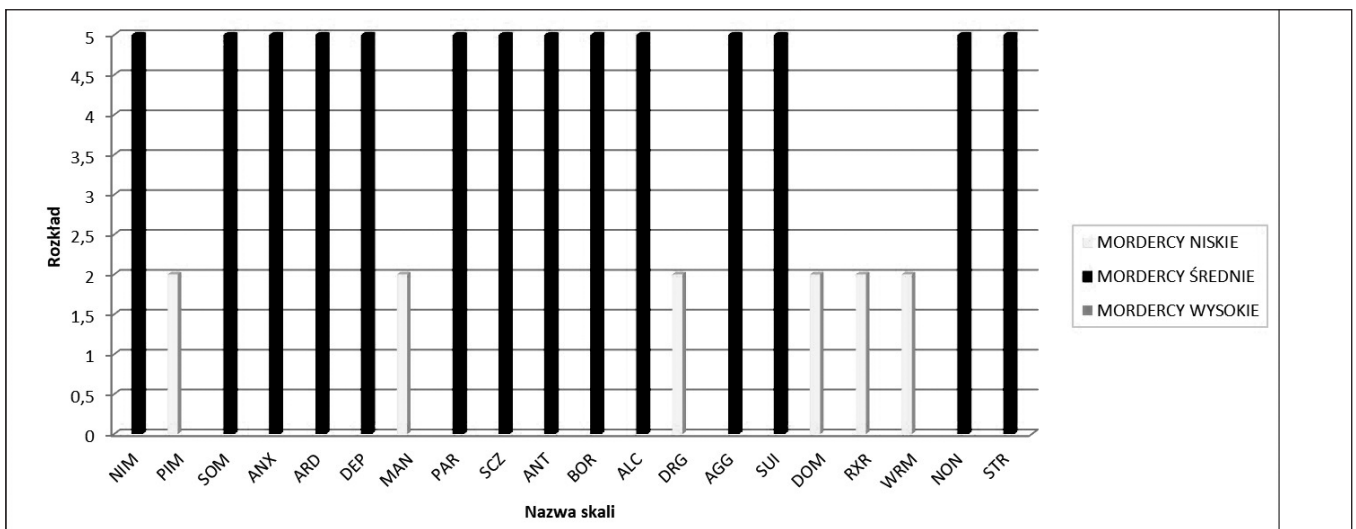
Celem badania było określenie zależności pomiędzy cechami osobowości a skłonnością do dokonywania różnych typów przestępstw: zabójstw, nękania, rozbojów, przestępstw na tle seksualnym, a także przestępstw mniejszego kalibru, jak np. załaganie z alimentami.



Ryc. 1. Stan cywilny przestępców a popełnione przez nich przestępstwo.



Ryc. 2. Poziom wykształcenia więźniów a popełnione przestępstwa.



Ryc. 3. Poziom uzyskanych wyników danych skal w poszczególnych grupach przestępców – mordercy.

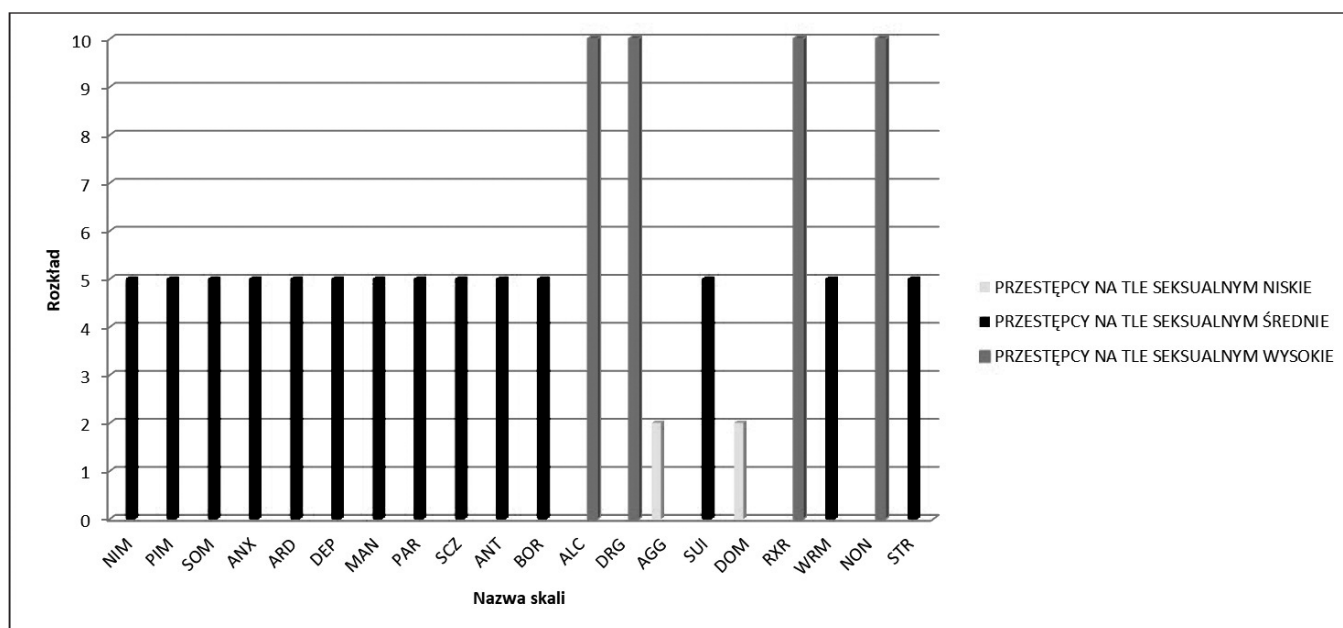
Poniższe opracowanie przedstawia wyniki badań przeprowadzone na 150 więźniach Zakładu Karnego w Nowym Wiśniczu, za pomocą testu PAI autorstwa L. C. Morey'a [5] do oceny osobowości i psychopatologii, w celu ustalenia korelacji między cechami osobowości przestępców a przestępstwem przez nich popełnionym. Osoby badane zaklasyfikowane do poszczególnych grup spełniają następujące kryteria: przynależność do danej grupy sprawców przestępstw:

- skazanych za morderstwo;
- skazanych za przestępstwa na tle seksualnym;
- skazanych za rozboje lub kradzieże;
- skazanych za zaleganie z alimentami;
- skazanych za znęcanie się.

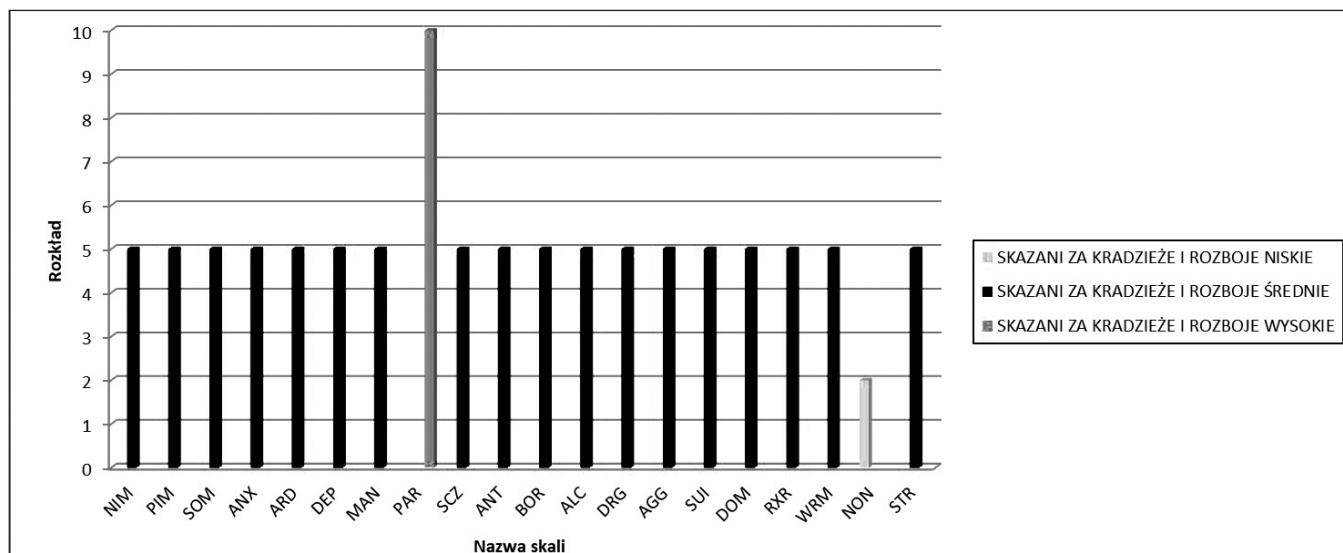
Każdy z przestępców reprezentuje konkretny, ściśle określony rodzaj przestępstwa.

GENEZA PROBLEMATYKI PRZESTĘPCZOŚCI

Z problemem przestępstw ludzkość zmagają się od czasów powstania pierwszych społeczności, a wraz z nimi pierwsze, niepisane kodeksy prawne. Określenie tego, co jest dobre a co złe ewoluuje od pokoleń [6]. Osoby łamiące prawo to sprawcy przestępstw. Różny jest charakter i nasilenie popełnianych wykroczeń, a to z kolei powoduje, że zapadają różne wyroki. Co sprawia, że przekroczone zostają normy prawne? Jedną z wielu przyczyn są cechy i zaburzenia



Ryc. 4. Poziom uzyskanych wyników danych skal w poszczególnych grupach przestępstw – przestępcy na tle seksualnym.



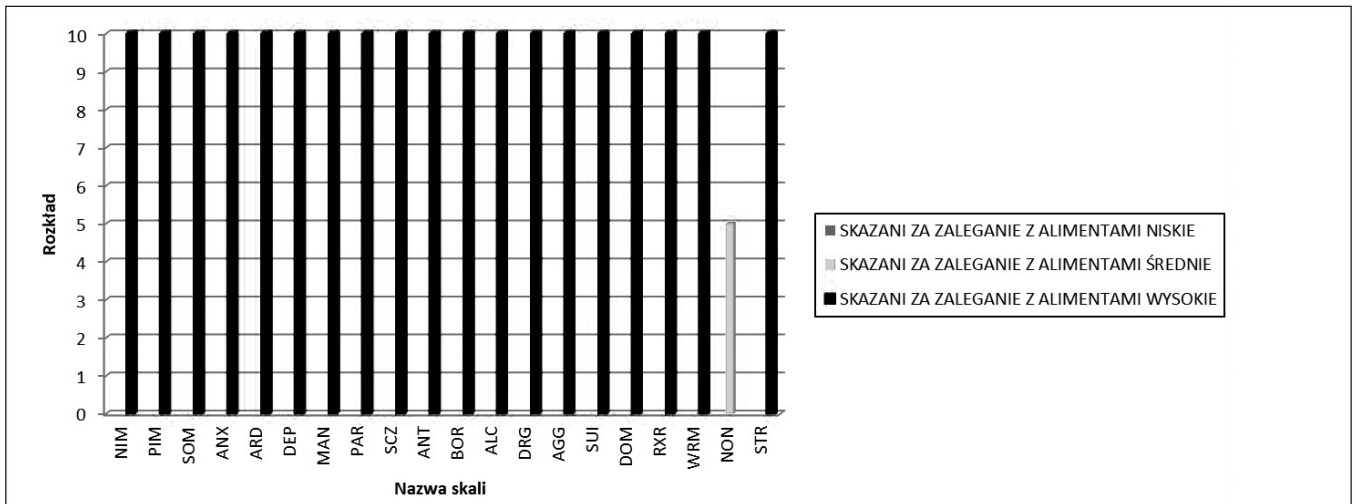
Ryc. 5. Poziom uzyskanych wyników danych skal w poszczególnych grupach przestępstw – przestępcy skazani za kradzieże, rozboje.

osobowości. I tak na przykład, jak wynika z badań, przestępcy na tle seksualnym mają przeważnie cechy narcyzyczne [7], mordercy neurotyczne [8].

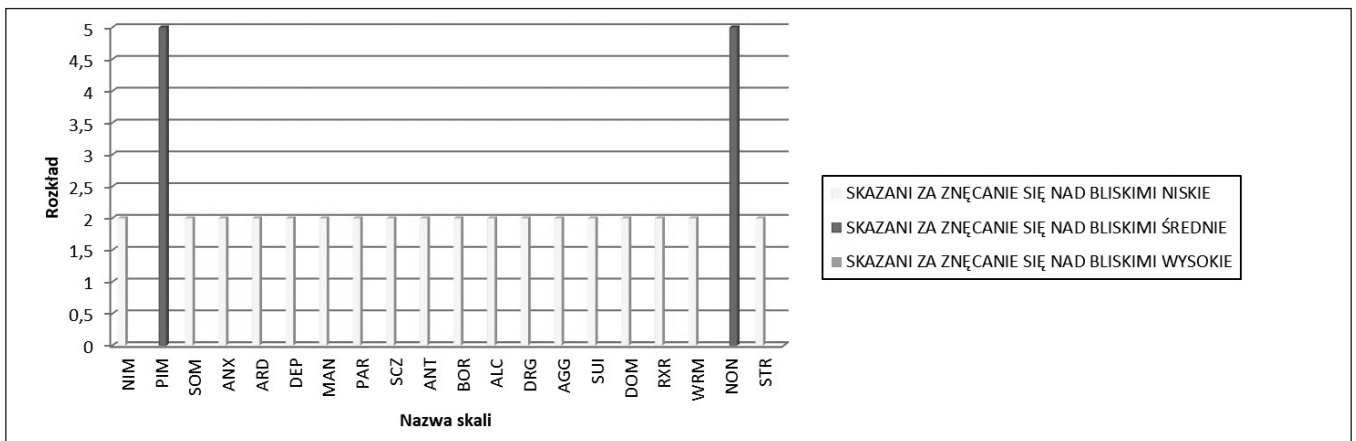
STATYSTYKI

Przestępczość to zjawisko patologiczne, polegające na działaniach niezgodnych z przyjętymi normami prawnymi, a zatem podlegające karze. W Polsce najczęściej badań nad zjawiskiem przestępczości zostało przeprowadzonych pod patronatem Instytutu Wymiaru Sprawiedliwości. Jednym z większych projektów były „Polskie Badania Przestępczości 07” wykonane na zlecenie Komendy Głównej Policji i prowadzone w 2007 roku, przez instytucje takie jak: Centrum Badania Opinii Publicznej, Pracownia Badań Społecznych DGA, TNS Ośrodek Badań Opinii Publicz-

nej. Badania te dotyczyły wiktylizacji. Wynika z nich, że poziom przestępczości w naszym społeczeństwie jest stosunkowo wysoki. Co piąty mieszkaniec Polski padł kiedyś ofiarą jakiegoś przestępstwa. Najniebezpieczniej jest w województwach dolnośląskim i mazowieckim (około 30% mieszkańców padło ofiarą przestępstwa), natomiast sytuacja wygląda odwrotnie w województwie świętokrzyskim (ofiarą przestępstwa padło jedynie 11,5%). Największe nasilenie zachowań przestępczych ma miejsce w już wspomnianych województwach dolnośląskim, mazowieckim, ale także zachodniopomorskim, natomiast najmniejsze w świętokrzyskim, lubelskim, podlaskim. Zgłaszalność przestępstw do instytucji, które zajmują się podejmowaniem działań w takich sytuacjach wynosi 50%. Co więcej badania pokazały, że poziom przestępczości na tle Unii Europejskiej jest także wysoki [9].



Ryc. 6. Poziom uzyskanych wyników danych skal w poszczególnych grupach przestępstw - przestępcy skazani za zaleganie z alimentami.



Ryc. 7. Poziom uzyskanych wyników danych skal w poszczególnych grupach przestępstw – przestępcy skazani za znęcanie się nad bliskimi.

Wiele instytucji podejmowało trud określenia, jak wysoki jest poziom przestępczości w różnych krajach. Jednymi z największych badań światowych są *National Crime Victimization Survey* (NCVS) oraz działający w Europie *British Crime Survey* (BCS). Cyklicznie prowadzone są badania *International Crime Victim Survey*. W latach 2007 – 2009 co szósty Polak padł ofiarą zachowań przestępczych [9].

OSOBOWOŚCIOWE UWARUNKOWANIA ZACHOWAŃ PRZESTĘPCZYCH

W Polsce mało przeprowadzano badań na temat cech osobowości, zaburzeń psychicznych więźniów. Jednymi z badań są badania R. Ł. Drwała [10, 11], który przeprowadził analizę, porównanie samoakceptacji i samooceny wśród młodzieży w zakładzie poprawczym. Kolejnymi są badania na Uniwersytecie Łódzkim, które opierały się o badanie korelatów osobowościowych więźniów w 1992 roku. W okresie od 1993 do 1996 zostały przeprowadzone badania więźniów przez J. Szałańskiego. Celem badań było określenie poczucia bezpieczeństwa, koherencji, sensu życia, osamotnienia, samorealizacji. Do badań użyto Kwestionariusza Poczucia Bezpieczeństwa (KPB) autorstwa Z. Uchnasta [11, 12,] i In-

wentarza Poczucia Bezpieczeństwa autorstwa A. Masłowa [11, 13]. Zbadano wówczas 150 więźniów, 30 grypsujących, 30 niegrypsujących [11, 14,] i 90 grypsujących, niegrypsujących i poszkodowanych [11, 15]. Z badań wynika, że więźniowie grypsujący mają wyższe poczucie bezpieczeństwa niż poszkodowani oraz niegrypsujący.

Udowodniono także, że osoby mniej inteligentne popełniają zabójstwa częściej. Główne cechy osobowości sprawców zabójstw to: egocentryzm, niewykształcona osobowość wyższa, nieprzystosowanie społeczne i niewykształcone postawy moralne, niski poziom świadomości społecznej, agresja, infantylnizm, nieumiejętność radzenia sobie ze samym sobą, chłód uczuciowy, labilność, brak empatii. Powyższe cechy są podstawą do stwierdzenia psychopatii. W przypadku mniejszego natężenia cech mamy do czynienia z zaburzeniami o cechach psychopatycznych, socjopatycznych [4].

Badania prowadzone przez A. Moir i D. Jessel wykazały, że agresywni psychopaci nie są zdolni do tworzenia prawidłowych związków międzyludzkich, brak im również empatii. Na podstawie wyników tych badań stwierdzić można także, że zabójcy mają pewne zakłócenia w funkcjonowaniu płątów czołowych, a także całego ośrodkowego układu nerwowego, to znaczy mają problemy neurologiczne [4].

Z kolei E. Czerwińska opisała syndromy zabójstwa i podzieliła je na: zaburzenie osobowości, niepokój, lęk, niską samokontrolę. Jednostki popełniające zbrodnie zazwyczaj wcześniej miały problemy zdrowotne, tzn. urazy czaszki. Do popełnienia tych czynów przyczynić się może złe środowisko wychowawcze czy też patologiczny poród, w czasie którego mogło dojść do uszkodzeń czaszkowo-mózgowych. Zabójcy charakteryzują się agresją, wrogością, egocentryzmem, ekstrawersją, dominacją [2-4].

Przestępców na tle seksualnym charakteryzuje: wrogość, egocentryzm, dominacja, nieumiejętność tworzenia satysfakcjonujących związków międzyludzkich. Najczęściej ich wychowanie przebiegało w warunkach korzystnych, nie charakteryzują ich także zaburzenia w sferze biologicznej [2-4]. Istnieje także syndrom sytuacyjny, który zakłada, że środowisko wychowawcze i zaburzenia biologiczne wpływające na funkcjonowanie mają związek z podejmowaniem zachowań przestępczych [2, 4, 16]. A. Szymusik i E. Leśniak [4, 17] podjęli próbę podziału zabójców na trzy grupy: chłodnych uczuciowo, nadpobudliwych emocjonalnie, odhamowanych (problemy z kontrolą zachowań na skutek zaburzeń ośrodkowego układu nerwowego).

Sprawcami przestępstw na tle seksualnym są głównie mężczyźni, a ofiarami kobiety. Z częstotliwością raz na rok ofiarą staje się mężczyzna, zgwałcony przez homoseksualistę. Ponownie należy stwierdzić, że to przestępstwo przypisuje się także osobom młodym. Przyczyną popełnienia tego przestępstwa są zaburzenia psychiczne i ogromny popęd seksualny młodych, którego nie są w stanie zahamować. W przypadku gdy oprawcą jest kobieta, jest to zjawisko tak zwanego wampiryzmu, który z kolei jest formą sadyzmu. Sprawcy ci najczęściej mają niską samokontrolę, są agresywni, mają niski poziom inteligencji, stanu wolnego [4].

PAI – PERSONALITY ASSESSMENT INVENTORY, JAKO METODA WYKORZYSTANA DO BADANIA

Test ten został przetłumaczony przez psychologa, pierwszą autorkę artykułu, z języka angielskiego na język polski i ponownie na język angielski (*back translation*) celem dokładnego oddania znaczenia itemów. Test został zaadaptowany do warunków polskich za zgodą autora amerykańskiego. Autorka sporządziła własne polskojęzyczne opracowanie, w dwóch wersjach, oddzielnej dla mężczyzn i oddzielnej dla kobiet, zawierające równocześnie metryczkę, kwestionariusz z 344 pytaniami oraz arkusz z czterema wariantami odpowiedzi. W celu usprawnienia analizy testu PAI autorka polskiej adaptacji wykonała projekt 42 przeźroczystych szablonów zawierających numery itemów wchodzących w skład poszczególnych skal i wartością punktową przyznawaną za udzieloną przez badanego na każde pytanie odpowiedź. Test PAI jeszcze nigdy do tej pory nie był użyty w Polsce. Autorka polskiej adaptacji wykorzystwała go po raz pierwszy w naszym kraju celem zbadania osobowości i psychopatologii osadzonych w Zakładzie Karnym w Nowym Wiśniczu w województwie małopolskim.

Zastosowanie tego testu po planowanej przez autorkę jego polskiej adaptacji wprowadzi nową jakość do badań

psychologicznych, rozszerzy spektrum możliwości psychologa. Przeprowadzone przy pomocy testu PAI badania wnoszą nowe opracowanie wyników badań, przez co stanowią uzupełnienie dotychczasowej wiedzy zgromadzonej na temat popełnianych przestępstw i przestępców je popełniających.

Opis metody: Kwestionariusz składa się z 344 pytań i 22 skal, czas badania – przeciętnie 50–60 minut.

Test PAI składa się z 22 nienakładających się na siebie skal związanych z szeroko zakrojonym problemem chorób psychicznych: 4 wiarygodności, 11 klinicznych, 5 terapeutycznych, 2 interpersonalnych.

SKALE:

SKALE WIARYGODNOŚCI:

Inconsistency (ICN) – skala niezgodności, bada, w jakim stopniu badany odpowiadał w ten sam sposób

Infrequency (INF) – skala rzadkich zjawisk, bada, w jakim stopniu respondenci uważają nietypowe wypowiedzi za prawdziwe

Negative Impression (NIM) – skala negatywnych wrażeń, bada stopień, w jakim badani przedstawiają się w negatywnym świetle

Positive Impression (PIM) – skala pozytywnych wrażeń, bada stopień, w jakim badani przedstawiają się w pozytywnym świetle

SKALE KLINICZNE:

Somatic concerns (SOM) – skala somatyczna – bada, mierzy problemy somatyczne i skargi na bóle badanego

Anxiety (ANX) – skala napięcia – bada lęk, niepokój, nerwowość, napięcie badanego

Anxiety Related Disorders (ARD) – skala zaburzeń lękowych – mierzy specyficzne objawy różnych zaburzeń lękowych

Depression (DEP) – skala depresji – mierzy odczucia badanego, uczucie smutku, osamotnienia, ospałości, oraz poczucie, że nie jest wart niczego

Mania (MAN) – skala manii – mierzy energię i pobudliwość badanego

Paranoia (PAR) – skala paranoi – służy do badania podejrzliwości respondenta

Schizophrenia (SCZ) – skala schizofrenii – bada niewyżądane doświadczenia i doznania badanego, ponadto jego dziwaczne myśli i obojętność społeczną

Borderline features (BOR) – skala *borderline* – bada konflikt między respondentem a jego tożsamością, niestabilność emocjonalną, problemy w relacjach społecznych

Antisocial features (ANT) – skala antyspołeczności – bada zachowania przestępcze i egoizm badanego

Alcohol Problems (ALC) – skala uzależnienia od alkoholu – bada problem nadmiernego spożywania alkoholu przez respondenta

Drug Problems (DRG) – skala uzależnienia od narkotyków – bada problem nadmiernego przyjmowania narkotyków, leków i używek

SKALE TERAPEUTYCZNE:

Aggression (AGG) – skala agresji – wskazuje na zachowania agresywne respondenta

Suicidal Ideation (SUI) – skala myśli samobójczych – mierzy częstotliwość, nasilenie i występowanie myśli samobójczych oraz jego planowanie

Nonsupport (NON) – skala izolacji społecznej – mierzy poziom izolacji społecznej, wycofania

Stress (STR) – skala stresu – mierzy poziom stresu, kontrolowanego i niekontrolowanego

Treatment rejection (RXR) – skala odrzucenia terapii – mierzy poziom motywacji badanego do terapii

SKALE INTERPERSONALNE:

Dominance (DOM) – skala dominacji – mierzy dominację badanego, asertywność

Warmth (WRM) – skala ciepła – mierzy poziom dobroci, zadowolenia, empatii, angażowanie się w sytuacje społeczne [1].

Podjęto wyzwanie zbadania rzetelności i trafności testu PAI w warunkach polskich, badając dwukrotnie tę samą grupę 40 kobiet i 40 mężczyzn żyjących na wolności, za pomocą α -Cronbacha i drugą metodą z użyciem metody test – retest w odstępach 4 tygodni, testami: PAI (L. C. Morey), EPQ - R (H. J. Eysenck i S. B. G. Eysenck) i PAI (L. C. Morey), NEO – FFI (P. T. Costa, R. R. McCrae).

W Stanach Zjednoczonych test ten używany jest do badania respondentów w trakcie psychoterapii, w sytuacjach kryzysowych, w celu ich oceny, w kryminalistyce, przy doborze pracowników, w ocenie bólu, w medycynie i ocenie przydatności do opieki nad dzieckiem [5].

WYNIKI BADAŃ

Zachowania przestępcze towarzyszą ludzkości od zarania dziejów. Naukowcy wielokrotnie podejmowali próby usystematyzowania wiedzy na ten temat. Pierwsza autorka pracy, będąc wolontariuszką w Zakładzie Karnym w Nowym Wiśniczu obserwowała skazanych. Zainteresowała ją zjawisko wpływu poszczególnych cech osobowości na rodzaj popełnianych przestępstw. Po wnikliwym zapoznaniu się z piśmiennictwem dotyczącym tego tematu postanowiła dokonać przeanalizowania związku pomiędzy cechami osobowości, zaburzeniami osobowości a rodzajem popełnianych czynów przestępczych. Badaniem objęto 150 więźniów, należących do 5 grup przestępstw, tj. morderców, przestępców na tle seksualnym, skazanych za kradzież i rozboje, zalegających z alimentami oraz znęcających się nad bliskimi.

Założeniem pracy było istnienie takiego związku. Wobec ograniczonej możliwości dostępnych w Polsce testów do badania osobowości i psychopatologii (badają one tylko jedną lub kilka cech osobowości) autorka postanowiła pozyskać od *Psychological Assessment Resources* test PAI, który dysponuje znacznie większymi możliwościami. Test ten został przetłumaczony przez autorkę pracy z języka angielskiego na język polski. Przeprowadzone również zostało *back translation*, retranslacja, czyli tłumaczenie

testu z języka polskiego na angielski celem sprawdzenia trafności dwukrotnego tłumaczenia przez autora testu, tak by pierwotna anglojęzyczna wersja była jednoznaczna z polskim tłumaczeniem polskiej adaptacji testu PAI. Test został przygotowany w dwóch oddzielnych wersjach dla kobiet i dla mężczyzn.

Istnieją również korelacje pomiędzy testem PAI oraz testami EPQ-R i NEO-FFI. Wszystkie skale testu PAI istotnie ujemnie korelują ze skalami K – kłamstwa i N – neurotyzmu testu EPQ-R. W przypadku testu NEO-FFI istotnie statystycznie koreluje dodatnio ze skalami: N – neurotyczności, U – ugodowości, S – sumienności oraz OTD – otwartości na doświadczenia, z którą koreluje 5 skal testu PAI (NIM – negatywnego wrażenia, SOM – somatyczna, DEP – depresji, smutku, osamotnienia, SCZ – niezwykłych doświadczeń badanego, dziwacznych myśli, STR – stresu). Rzetelność arkusza testu PAI z kolei mieści się w przedziale 0,65–0,95, co oznacza wysoką zgodność i rzetelność testu w warunkach polskich badań. Wewnętrzna zgodność testu badana dwukrotnie w teście i reteście wynosi $\alpha=0,98$. Nie można by zatem podnieść rzetelności testu PAI. Zmiana poszczególnych itemów testu także nie przyniosłaby korzyści.

Z przeprowadzonej analizy wynika, że test PAI oddaje istotę zagadnienia. Dostarcza dowodów na istnienie związku pomiędzy cechami osobowości, stanami psychicznymi i zaburzeniami osobowości a konkretnym rodzajem popełnianych przestępstw.

W ten sposób, wykorzystując test PAI, uzyskano możliwość posłużenia się 22 nienakładającymi się na siebie skalami i ich podskalami w celu zbadania szerokiego problemu chorób psychicznych. Test ten zawiera 4 skale wiarygodności, 11 klinicznych, 5 terapeutycznych, 2 interpersonalne. Poza tym skale badają: zaburzenia nerwicowe, zaburzenia psychotyczne, problemy kontroli impulsów, czynniki potencjalnej szkodliwości wobec siebie i innych, miarę warunków środowiskowych i motywację do leczenia, ciepło partnerskie vs. zimne oddalanie się i styl dominujący/kontrolujący vs. styl uległy, osobowość z pogranicza, osobowość chwiejną emocjonalnie typu *borderline*, zachowania i cechy antyspołeczne.

Celem pracy było ustalenie, czy istnieje związek pomiędzy cechami osobowości, a rodzajem popełnionego czynu zabronionego przez prawo oraz ustalenie, jakie cechy osobowości są charakterystyczne dla sprawcy danego typu przestępstwa.

Ustalono zależność pomiędzy charakterem przestępstwa a specyficznymi cechami osobowości, stanem cywilnym oraz poziomem wykształcenia przestępców (Ryc. 1–2).

Ustalono, że istnieje związek pomiędzy cechami osobowości więźnia, a czynem jakiego się dopuścił (Ryc. 3–7).

Najbardziej zróżnicowaną zmienną w badaniu były lata spędzone w więzieniu, które u morderców wahały się od 0,5 roku do 32 lat, u skazanych za przestępstwa na tle seksualnym od 0,5 roku do 16 lat, u skazanych za kradzież i rozboje od 0,5 roku do 16 lat, u zalegających z alimentami od 1 roku do 9 lat, u przestępców znęcających się nad bliskimi od 8 miesięcy do 18 lat.

Cechami charakterystycznymi dla morderców są: uzależnienie od narkotyków, mania, dominacja, ciepło, odrzucenie terapii.

Cechami charakterystycznymi dla przestępców na tle seksualnym są: agresja, uzależnienie od alkoholu, narkotyków, paranoja, izolacja społeczna.

Cechami charakterystycznymi dla skazanych za kradzież i rozboje są: paranoja, izolacja społeczna.

Cechami charakterystycznymi dla skazanych za zaleganie z alimentami są: agresja, uzależnienie od alkoholu, problemy somatyczne, lęk, zaburzenia lękowe, paranoja, typ osobowości *borderline*, antyspołeczność, schizofrenia, mania, depresja, stres, dominacja, ciepło, myśli samobójcze.

Cechami charakterystycznymi dla skazanych za znęcanie się nad bliskimi są: agresja, uzależnienie od alkoholu, problemy somatyczne, lęk, uzależnienie od narkotyków, zaburzenia lękowe, paranoja, typ osobowości *borderline*, antyspołeczność, schizofrenia, mania, stres, dominacja, ciepło, odrzucenie terapii, myśli samobójcze.

PODSUMOWANIE

Zastosowanie testu PAI po planowanej przez pierwszą autorkę jego polskiej adaptacji wprowadzi nową jakość do badań psychologicznych, rozszerzy spectrum możliwości psychologa. Przeprowadzone przy pomocy testu PAI badania wnoszą nowe opracowanie wyników badań przez co stanowią uzupełnienie dotychczasowej wiedzy zgromadzonej na temat popełnianych przestępstw i osób je popełniających.

Niewiele mamy badań na ten temat, więc porównanie ich z innymi doniesieniami sprawia wyjątkową trudność. Literatura przedmiotu jest skąpa, więc nie jest możliwe przedstawienie porównania badań przeprowadzonych przez autorów polskiej adaptacji testu PAI z innymi badaniami dotyczącymi tego tematu przeprowadzonymi w Polsce czy na świecie.

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Nadesłano: 07.01.2018

Zaakceptowano: 05.02.2018

ZALECENIA EULAR DOTYCZĄCE TERAPII RZS – AKTUALIZACJA Z 2016 ROKU

EULAR RECOMMENDATION FOR RA THERAPY – UPDATE FROM 2016

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STRESZCZENIE

Zalecenia dotyczące terapii reumatoidalnego zapalenia stawów (RZS) znacząco zmieniały się w ciągu ostatnich 30 lat. Zalecenia te w ciągu ostatniej dekady stawały się coraz bardziej złożone. Niezmiennie jednak dąży się do remisji lub niskiej aktywności choroby. Pożądane jest osiągnięcie niskiej aktywności choroby w ciągu 6 miesięcy terapii i przynajmniej 50% poprawy w przeciągu 3 miesięcy. Jednak wysokie koszty nowych terapii utrudniają i ograniczają wdrażanie skutecznych strategii leczenia. W poniższej pracy przedstawiono aktualizację zaleceń EULAR opracowaną w 2016 roku przez międzynarodowy panel ekspertów.

SŁOWA KLUCZOWE: reumatoidalne zapalenie stawów, strategia leczenia, leki modyfikujące przebieg choroby

ABSTRACT

Recommendations for rheumatoid arthritis (RA) therapy have changed significantly over the last 30 years. Over the last decade, these recommendations have become more and more complex. Invariably, remission or low disease activity is the goal of RA therapy. It is desirable to achieve a low disease activity within 6 months of treatment and at least 50% improvement over the 3 months. However, the high costs of new therapies make it difficult and restrict the implementation of effective treatment strategies. The following paper presents the update of EULAR recommendations elaborated in 2016 by the international panel of experts.

KEY WORDS: rheumatoid arthritis, treatment strategy, disease-modifying antirheumatic drugs

(Tłumaczenie na język polski ze Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-977) [1].

Wiad Lek 2018, 71, 1 cz. II, 237-243

WSTĘP

Pierwsze zalecenia EULAR powstały w 2010 r., a zostały zaktualizowane w 2013 r. W ubiegłym roku międzynarodowy panel złożony z 50 ekspertów (pacjenci, reumatolodzy, pracownicy służby zdrowia) w dziedzinie reumatologii, w oparciu o rozliczne dane, opracował kolejną aktualizację istniejących wytycznych. Najnowsze zalecenia uwzględniają efektywność kliniczną i funkcjonalną, bezpieczeństwo, koszty terapii, a także stosunek pacjentów do leczenia. Szczególną uwagę poświęcono kwestii bezpieczeństwa stosowania leków antyreumatycznych, głównie ryzyku infekcji oraz szczepieniom. W zaleceniach nie rozróżnia się wczesnego i zaawansowanego RZS. Podkreślana jest jednak potrzeba wdrożenia terapii we wczesnych etapach schorzenia. Uwaga skupiona jest na fazach procesu leczenia i różnicuje pacjentów na grupy: niepoddawanych wcześniej terapii DMARD, grupę z niewystarczającą odpowiedzią na pierwszą strategię leczenia konwencjonalnymi syntetycznymi lekami modyfikującymi przebieg choroby (csDMARD) i grupę z niewystarczającą

odpowiedzią na leczenie biologicznymi lekami modyfikującymi przebieg choroby (bDMARD). Panel ekspertów doprecyzował również znaczenie poszczególnych terminów (Tab I.).

Aktualne zalecenia dotyczą pacjentów z rozpoznaniem RZS, nie stanów przed RZS lub niezróżnicowanego zapalenia stawów. Poniżej przedstawiono aktualnie obowiązujące zalecenia EULAR dotyczące terapii RZS (Tab II.)

NADRZĘDNE ZASADY TERAPII RZS

A. LECZENIE POWINNO SIĘ OPIERAĆ NA WSPÓLNEJ DECYZJI I POROZUMIENIU POMIĘDZY LEKARZEM I PACJENTEM, ORAZ POWINNO DĄŻYĆ DO ZAPEWNIENIA CHOREMU JAK NAJLEPSZEJ OPIEKI
Zasada ta dotyczy wszystkich aspektów choroby, począwszy od diagnozy i poinformowania pacjenta o chorobie (włą-

Tabela I. Podstawowe definicje używane w wytycznych EULAR 2016 r.

Syntetyczne DMARD	Konwencjonalne syntetyczne DMARD (csDMARD) jak metotreksat, leflunomid, sulfasalazyna, hydroksychlorochina Celowane syntetyczne DMARD (tsDMARD) jak tofacitinib, baricitinib
Biologiczne DMARD	Oryginalne biologiczne DMARD (boDMARD) Biopodobne DMARD (bsDMARD)
Glikokortykosteroidy	GC
Stadia aktywności choroby	Remisja – stan oceniany w oparciu o wskaźniki [2] Niska aktywność – stan oceniany w oparciu o wskaźniki [3–5] Średnia aktywność Wysoka aktywność
Złe czynniki prognozy	Umiarkowana (po leczeniu csDMARD) lub wysoka aktywność choroby; Wysoki poziom wskaźników ostrej fazy Liczne obrzęknięte stawy; Obecność czynnika RF i/lub ACPA (zwłaszcza ich wysokie miano); Wczesne nadżerki w stawach Niepowodzenie terapii dwoma lub więcej csDMARD
Redukcja terapii	Ograniczenie – zmniejszenie dawki leku lub wydłużenie przerw pomiędzy przyjmowanymi dawkami leku; może dotyczyć również zaprzestania przyjmowania leku, ale dopiero po stopniowym i powolnym zmniejszaniu dawki; Zaprzestanie – przerwanie przyjmowania leku

czając edukację w zakresie przyczyn, przebiegu i zagrożeń jakie niesie ze sobą schorzenie), sposobach oceny stanu choroby, terapii i celu terapeutycznego a także opracowania planu leczenia. Omówione powinno również zostać ryzyko i korzyści, jakie niosą ze sobą poszczególne rodzaje terapii. Aby zasięgnąć szczegółowych informacji w odniesieniu do poszczególnych aspektów, należy zapoznać się ze standardami opieki [6]. Aby móc mówić o wspólnej decyzji pacjenta i lekarza, należy odnieść się do wskaźników jakości [7].

B. DECYZJE DOTYCZĄCE LECZENIA MUSZĄ BYĆ PODEJMOWANE NA PODSTAWIE WSKAŹNIKÓW CHOROBY TAKICH JAK: JEJ AKTYWNOŚĆ, USZKODZENIA STRUKTURALNE, WSPÓLISTNIENIE INNYCH SCHORZEŃ I BEZPIECZEŃSTWO PACJENTA

Zasada druga została wprowadzona do obecnych zaleceń i wynika z poprzedniej wersji wytycznych z 2013 r. Ustalono, że powinna ona wręcz stanowić nadrzędną regułę, a nie tylko zalecenie. Leczenie choroby jest oparte na szeregu wskaźników, takich jak: aktywność choroby, zmiany strukturalne tkanek, współwystępowanie innych schorzeń a także kwestii bezpieczeństwa pacjenta.

C. LECZENIEM SCHORZENIA POWINIEN ZAJMOWAĆ SIĘ REUMATOLOG

To reumatolog jest specjalistą posiadającym najlepsze przygotowanie do zapewnienia pacjentowi właściwej opieki w zakresie wczesnego rozpoczęcia terapii, zapobiegania uszkodzeniom tkanek i minimalizacji zabiegów chirurgicznych. Ci specjaliści mają również najbardziej obszerne doświadczenia w zakresie leczenia DMARDs (zarówno konwencjonalnymi syntetycznymi,

jak i biologicznymi), które obejmują profil działań niepożądanych oraz ich zastosowanie przy chorobach współlistniejących z RZS. Dlatego to właśnie reumatolog jest osobą zdolną do zapewnienia „najlepszej opieki”, która jest zaleceniem A.

Zgodnie z poprzednią wersją wytycznych, opieka ta powinna mieć charakter multidyscyplinarny i obejmować również udział specjalistycznych pielęgniarek, a przy chorobach współlistniejących (jak przewlekłe zapalenie wątroby lub śródmiąższowa choroba płuc) konsultacji i leczenia innych specjalistów.

D. REUMATOLOG POWINIEN UWZGLĘDNIĆ W TERAPII JEJ KOSZTY INDYWIDUALNE, MEDYCZNE I SPOŁECZNE

Wdrożenie skutecznej terapii, pomimo kosztów bezpośrednich, zmniejsza obciążenia ekonomiczne pacjenta, rodziny i społeczeństwa (opóźnia niezdolność do pracy, przejście na przedwczesną emeryturę). Należy przy tym mieć świadomość, że realne koszty terapii RZS są niewspółmierne i przekraczają koszty wynikające z leczenia widocznych objawów RZS (należy uwzględnić choćby koszty leczenia chorób współlistniejących i związanych z procesem zapalnym). Należy mieć świadomość, że w niektórych krajach koszty leczenia są istotnym czynnikiem limitującym dostęp do skutecznych terapii. Niestety, pomimo stosowania nowych terapii i strategii terapeutycznych, wielu pacjentów nadal nie osiąga założonych celów terapeutycznych. Dowodzi to, że nadal istnieje potrzeba poszukiwania nowych terapii i strategii terapeutycznych.

W stosunku do poprzednich, wytyczne EULAR 2016 zawierają 12 zaleceń (o dwa mniej niż poprzednio). Zostały one również w dużej mierze zmodyfikowane. 12

Tabela II. Zalecenia EULAR z 2016r [za 1].

Zasady nadrzędne	
A.	Leczenie pacjentów z RZS powinno mieć na celu zapewnienie najlepszej opieki i być oparte o wspólną decyzję pacjenta i reumatologa
B.	Decyzje dotyczące leczenia muszą być podejmowane na podstawie wskaźników choroby, takich jak: jej aktywność, uszkodzenia strukturalne, współistnienie innych schorzeń i bezpieczeństwo pacjenta
C.	Reumatolodzy są specjalistami, którzy przede wszystkim powinni zapewnić opiekę pacjentom z RZS
D.	Reumatolog powinien w leczeniu RZS rozważyć koszty indywidualne, medyczne i społeczne
Zalecenia	
1.	Terapię DMARD należy rozpocząć natychmiast po rozpoznaniu RZS
2.	Leczenie powinno mieć na celu osiągnięcie trwałej remisji lub niskiej aktywności choroby u każdego pacjenta.
3.	Monitorowanie choroby powinno mieć miejsce częściej w przypadku aktywnej choroby (co 1–3 miesiące); jeśli poprawa nie nastąpi po co najmniej 3 miesiącach od rozpoczęcia terapii lub cel terapeutyczny nie zostanie osiągnięty przez 6 miesięcy, należy skorygować podjęte leczenie
4.	Metotreksat (MTX) powinien być częścią pierwszej strategii leczenia
5.	U pacjentów z przeciwwskazaniami (lub wczesną nietolerancją) do stosowania MTX, jako część pierwszej strategii leczenia, należy rozważyć zastosowanie leflunomidu lub sulfasalazyny
6.	Podczas włączania lub zmiany csDMARDs należy rozważyć krótkoterminowe zastosowanie GC (przy różnym reżimie dawkowania i drogach podawania), jednak powinno ono być ograniczane tak szybko jak to możliwe z klinicznego punktu widzenia
7.	Jeśli cel terapeutyczny nie zostanie osiągnięty przy zastosowaniu pierwszej strategii terapeutycznej z wykorzystaniem csDMARD, przy braku złych czynników prognozy, należy rozważyć zastosowanie innych csDMARD
8.	Jeśli cel terapeutyczny nie zostanie osiągnięty przy zastosowaniu pierwszej strategii terapeutycznej z wykorzystaniem csDMARD, w przypadku występowania złych czynników prognozy, należy rozważyć dodanie do schematu leczenia bDMARD lub tsDMARD; w obecnej praktyce włącza się bDMARD
9.	bDMARD i tsDMARD powinny być kojarzone z csDMARD; w przypadku pacjentów, którzy nie mogą stosować csDMARDs inhibitory szlaku IL-6 i tsDMARD mogą być korzystniejsze w porównaniu do bDMARD
10.	Jeśli terapia bDMARD lub tsDMARD okaże się nieskuteczna, należy zastosować inny bDMARD lub tsDMARD; jeśli terapia inhibitorem TNF okaże się nieskuteczna, można zastosować inny inhibitor TNF lub preparat o innym mechanizmie działania
11.	Jeśli pacjent, po ograniczeniu terapii GC, znajduje się w stanie stałej remisji, można rozważyć ograniczenie przyjmowania bDMARD, zwłaszcza jeśli stosowana jest terapia w skojarzeniu z csDMARD
12.	Jeśli pacjent znajduje się w stanie stałej remisji, można rozważyć ograniczenie terapii csDMARD

aktualnych zaleceń tworzy logiczną całość, poczynając od konieczności zainicjowania skutecznej terapii, określenia celu terapeutycznego i oceny choroby oraz dążenia do tego celu. W oparciu o dostępne leki oraz zatwierdzone czynniki prognostyczne, opracowano algorytm postępowania w terapii RZS (Ryc. 1). Zalecenia są perspektywiczne i obejmują również leki, które przeszły badania III fazy (ich stosowanie jest uzależnione od statusu zatwierdzenia w poszczególnych krajach).

Zalecenia wskazują na dążenie do ograniczenia stosowania leków lub nawet wycofania niektórych w sytuacji, gdy cel terapeutyczny został osiągnięty i powinno się go jedynie podtrzymywać. Poniżej omówiono dokładniej każde z 12 zaleceń indywidualnych.

1. TERAPIĘ DMARD NALEŻY ROZPOCZĄĆ NATYCHMIAST PO ROZPOZNANIU RZS

Zalecenie to nie uległo zmianie w stosunku do roku 2013 i jest jednym z podstawowych podejść do terapii choroby. Wiąże się

ono z koniecznością jak najszybciej postawionego rozpoznania. Pozwala to w dużej mierze zapobiegać uszkodzeniom strukturalnym u pacjentów. Przy czym nie został tu wskazany konkretny preparat, jako że zastosowanie różnorodnych leków z tej grupy na wczesnym etapie choroby pozwala na osiągnięcie dobrych rezultatów długoterminowych, w porównaniu do zastosowania ich w stadium zaawansowanym. Sekwencje poszczególnych terapii DMARD zostały omówione szczegółowo w kolejnych punktach. W zaleceniu nie rozpatrywano stadiów przed rozpoznaniem RZS lub niezróżnicowanego zapalenia stawów. Jednak jakiegokolwiek przewlekłe zapalenie stawów wymaga odpowiedniej terapii, w tym DMARD (zalecenia dotyczące terapii wczesnego zapalenia stawów zostały omówione gdzie indziej [8]).

2. TERAPIA RZS POWINNA MIEĆ NA CELU TRWAŁĄ REMISJĘ LUB OSIĄGNIĘCIE TRWAŁEGO STANU NISKIEJ AKTYWNOŚCI CHOROBY U KAŻDEGO PACJENTA

Zalecenie dotyczy dwóch celów: remisji, zwłaszcza u pacjentów wcześniej nieleczonych DMARD oraz niskiej aktywności

choroby, głównie u pacjentów, u których wcześniejsze leczenie nie przyniosło rezultatów. Jakikolwiek inny stan aktywności choroby (poza remisją i niską aktywnością) jest powodem do rozważenia zmiany terapii, jeśli inne czynniki nie wykluczają tego. Bardzo istotna jest komunikacja z pacjentem w celu odpowiedniej edukacji i zwiększenia stosowania się pacjenta do zaleceń terapii, co przekłada się na wzrost prawdopodobieństwa osiągnięcia celu terapeutycznego. Cel leczenia powinien zostać osiągnięty szybko. Istnieją dowody, że większość pacjentów, która nie osiągnęła znaczącej poprawy w ciągu pierwszych 3 miesięcy terapii lub nie osiągnięto celu leczenia w ciągu 6 miesięcy, nie osiągnie jej i później. Wyjątki dotyczą tych pacjentów, u których aktywność choroby została zmniejszona do poziomu bliskiego celowi leczenia.

Stan remisji koreluje z brakiem podklinicznego zapalenia błony maziowej w rezonansie magnetycznym i w ultrasonografii oraz braku progresji w kierunku uszkodzenia stawu. Stan choroby powinien być definiowany w oparciu o indeksy SDAI i CDAI. Można je stosować również w przypadku terapii lekami skierowanymi przeciwko białkom odpowiedzi ostrej fazy.

Również niska aktywność choroby powinna być odpowiednio mierzona. Jednak w przypadku stosowania leków, które oddziałują na białka odpowiedzi ostrej fazy (inhibitory cytokin, zwłaszcza interleukiny 6 lub inhibitory kinazy Jak), zastosowanie wskaźnika DAS28 może nie być wystarczająco wiarygodne.

Cel terapeutyczny powinien być osiągnięty trwale. Przy tym termin „trwały” nie został jeszcze doprecyzowany. Proponowano, że powinien wynosić co najmniej 6 miesięcy.

3. MONITOROWANIE CHOROBY POWINNO MIEĆ MIEJSCE CZĘŚCIEJ W PRZYPADKU AKTYWNEJ CHOROBY (CO 1-3 MIESIĄCE); JEŚLI POPRAWA NIE NASTĄPI PO CO NAJMNIEJ 3 MIESIĄCACH OD ROZPOCZĘCIA TERAPII LUB CEL TERAPEUTYCZNY NIE ZOSTANIE OSIĄGNIĘTY PRZEZ 6 MIESIĘCY, NALEŻY DOSTOSOWAĆ PODJĘTE LECZENIE

Zalecenie to nie zostało zmienione w stosunku do poprzedniej wersji z 2013 roku. Częstość badań uzupełniających powinna być dostosowana do poziomu aktywności choroby i częsta np. raz w miesiącu, kiedy pacjent na wysoką aktywność choroby; i rzadsza, np. co 6 – 12 miesięcy, kiedy cel leczenia został osiągnięty. Zmiana stanu choroby powinna zostać osiągnięta po 3 miesiącach terapii. Poprawa o 50%, oceniana poprzez złożony system oceny, daje szansę na osiągnięcie celu terapeutycznego. Aby móc ocenić postępy w terapii, zaleca się porównanie aktywności choroby w stosunku do stanu wyjściowego.

Dostosowanie terapii obejmuje optymalizację dawki lub drogi podania leku (MTX lub inny DMARD) albo iniekcje stawów glikokortykosteroidami; i odnosi się tylko do sytuacji gdy leczenie nie przynosiło rezultatów.

4. MTX POWINIEN BYĆ CZĘŚCIĄ PIERWSZEJ STRATEGII LECZENIA

Zalecenie zostało nieznacznie skrócone w porównaniu do 2013 roku. Ze względu na skuteczność, bezpieczeństwo

(zwłaszcza w obecności kwasu foliowego), możliwości indywidualizacji dawki i sposobu podania leku, a także stosunkowo niskich kosztów, MTX nadal stanowi lek pierwszej linii, zarówno w monoterapii, jaki i w skojarzeniu z innymi preparatami. Stosowanie MTX wydaje się zmniejszać śmiertelność w RZS. W porównaniu do terapii bDMARD, monoterapia MTX pacjentów z wczesnym zapaleniem stawów była związana z odpowiedzią ACR70 u 25% pacjentów (która prowadzi do niskiej aktywności choroby) w ciągu 6 miesięcy, pomimo że nie włączono GC. Dawkę MTX należy szybko zwiększać, zwykle do 25–30 mg/tydzień, doustnie lub podskórnie, z suplementacją kwasem foliowym. Aby móc wiarygodnie ocenić odpowiedź na leczenie, dawka minimalna, jeśli jest tolerowana, powinna zostać utrzymana przez 8–12 tygodni. Przy zwiększaniu dawki do 25 mg tygodniowo, odsetek odpowiedzi może być wyższy (około 40% niskiej aktywności choroby). Należy przy tym wziąć pod uwagę przeciwwskazania i toksyczność leku. Powinno się także pamiętać, że wspomniane dawki nie dotyczą pacjentów azjatyckich. W Chinach nie zaleca się stosowania 20 mg tygodniowo, a w Japonii maksymalna dawka leku wynosi 16 mg/tydzień.

Z zalecenia usunięto sformułowanie mówiące, że csDMARD w monoterapii lub terapii skojarzeniowej powinny być stosowane u pacjentów niepoddawanych wcześniej leczeniu DMARD, niezależnie od podawania GC. Rozważano wyższą częstość działań niepożądanych, często łagodnych, przy stosowaniu terapii skojarzeniowej. Może to wykluczać zwiększanie dawek niektórych leków. Nie znaleziono również jednoznacznych dowodów na przewagę skuteczności terapii skojarzeniowej w porównaniu z monoterapią csDMARD. Nie wyklucza to naturalnie stosowania terapii skojarzeniowej, ale powinna to być wspólna decyzja pacjenta i lekarza, po uwzględnieniu wszystkich zalet i wad takiego leczenia. W przypadku terapii skojarzonej należy mieć świadomość, że przed włączeniem bDMARD w niektórych krajach, preferowane jest zastosowanie dwóch csDMARD.

5. U PACJENTÓW Z PRZECIWSKAZANIAMI (LUB WCZESNĄ NIETOLERANCJĄ) DO STOSOWANIA MTX, JAKO CZĘŚĆ PIERWSZEJ STRATEGII LECZENIA NALEŻY ROZWAŻYĆ ZASTOSOWANIE LEFLUNOMIDU LUB SULFASALAZYNY

Treść tego zalecenia została utrzymana, z doprecyzowaniem terminu „z przeciwwskazaniami do stosowania MTX”. Zwrócono ponownie uwagę na dużą rolę omówienia z pacjentem ustalonej terapii, aby móc uspokoić jego obawy (wielu pacjentów po przeczytaniu ulotki ma wątpliwości co do leczenia, ze względu na strach przed wymienionymi w ulotce działaniami niepożądanymi). Przy rzeczywistych przeciwwskazaniach (np. współwystępowaniu choroby nerek lub wątroby) lub nietolerancji MTX, dobrym rozwiązaniem jest zastosowanie leflunomidu (w dawce 20 mg na dobę, bez dawki nasycającej) lub sulfasalazyny (w dawce zwiększanej do 3 g na dobę). Należy pamiętać, że spośród wspomnianych preparatów tylko sulfasalazyna ma profil bezpieczeństwa pozwalający na stosowanie w trakcie ciąży.

Podobnie jak w przypadku MTX, leflunomid i sulfasalazyna mogą być stosowane w monoterapii lub w skojarzeniu z innymi csDMARD lub lekami biologicznymi i w tym ostatnim przypadku jest często stosowana.

6. PODCZAS WŁĄCZANIA LUB ZMIANIE csDMARDS NALEŻY ROZWAŻYĆ KRÓTKOTERMINOWE ZASTOSOWANIE GLIKOKORTYKOSYTEROIDÓW (PRZY RÓŻNYM REŻIMIE DAWKOWANIA I DROGACH PODAWANIA), JEDNAK POWINNO ONO BYĆ OGRANICZANE TAK SZYBKO JAK TO MOŻLIWE Z KLINICZNEGO PUNKTU WIDZENIA

Dowiedziano zwiększoną skuteczność terapii csDMARD w skojarzeniu z GC. Jest ona porównywalna ze skutecznością terapii csDMARD + bDMARD.

W porównaniu do zaleceń z 2013r. zalecenie przesunięto (poprzednio było w punkcie 7) i zmodyfikowano (poprzednio można było rozważyć stosowanie GC w małej dawce jako leczenie początkowe (w skojarzeniu z jednym lub większą liczbą csDMARD) przez okres do 6 miesięcy, ale powinno być ograniczane tak szybko jak to możliwe). Obecny zapis stanowi kompromis pomiędzy skutecznością takiej terapii a jej zagrożeniami. Zgodzono się, że w terapii nie należy stosować dużych dawek GC przez dłuższy czas. Jako niską dawkę przyjęto 7,5 mg lub mniej prednizolu na dobę. Badania kliniczne dowiodły skuteczności krótkotrwałego podawania GC w małych dawkach, poniżej 7,5 mg na dobę, z dawką wysycającą 30 mg przy podaniu doustnym, 120 mg metyloprednizolu w pojedynczym wstrzyknięciu domięśniowym lub 25 mg preparatu w jednorazowej iniekcji dożylniej. Z powodu tej różnorodności w obecnych zaleceniach termin „niska dawka” został skreślony. z kolei wprowadzono sformułowanie umożliwiające reumatologowi oraz pacjentowi wybór drogi podania i reżimu dawkowania.

Dużo kontrowersji wzbudził wybór optymalnego sposobu dawkowania. Sugerowano, że jednorazowe podanie dożylnie lub domięśniowe przekłada się na znacznie niższą dawkę kumulacyjną niż kilka tygodni doustnego podawania małej dawki. Jednak pogląd ten nie zyskał pełnej akceptacji członków zespołu dyskusyjnego. GC powinny być rozważane na równi z csDMARD, zarówno jako część terapii początkowej lub późniejszej, jeśli początkowa się nie powiedzie. Zwykle jednak GC nie są potrzebne jako terapia pomostowa, jeśli stosowane jest leczenie bDMARD lub tsDMARD. Należy pamiętać o tym, że GC zwykle mają gwałtowne działanie i zwiększają ryzyko infekcji. Zaleca się stosowanie GC wraz z csDMARD jako terapię pomostową do czasu osiągnięcia maksymalnego efektu działania csDMARD (przy zastosowaniu konkretnego jednego sposobu dawkowania), a następnie stopniowo zmniejszać dawkę leku. Zmodyfikowano też algorytm terapii, zmieniając \pm na + przy możliwości stosowania GC (Ryc. 1).

Dawkę GC należy zmniejszać i ostatecznie wycofać całkowicie w ciągu 3 miesięcy od rozpoczęcia terapii lub wyjątkowo w ciągu 6 miesięcy. Długotrwałe stosowanie GC w dawkach powyżej 5 mg na dobę niesie ze sobą szereg zagrożeń.

Jeśli GC nie mogą zostać wycofane z terapii, leczenie DMARD może być rozważane jako nieskuteczne.

7. JEŚLI CEL TERAPEUTYCZNY NIE ZOSTANIE OSIĄGNIĘTY PRZY ZASTOSOWANIU PIERWSZEJ STRATEGII TERAPEUTYCZNEJ Z WYKORZYSTANIEM csDMARD, PRZY BRAKU ZŁYCH CZYNNIKÓW PROGNOZY, NALEŻY ROZWAŻYĆ ZASTOSOWANIE INNYCH csDMARD

Nie powinno się kojarzyć różnych csDMARD w pierwszej strategii leczenia. Nie należy też rozpatrywać wczesnej nietolerancji csDMARD od razu jako niepowodzenia w leczeniu i przenosić pacjenta do drugiej fazy algorytmu. Powinno się raczej zastąpić stosowany csDMARD innym preparatem z tej grupy.

8. JEŚLI CEL TERAPEUTYCZNY NIE ZOSTANIE OSIĄGNIĘTY PRZY ZASTOSOWANIU PIERWSZEJ STRATEGII TERAPEUTYCZNEJ Z WYKORZYSTANIEM csDMARD, W PRZYPADKU WYSTĘPOWANIA ZŁYCH CZYNNIKÓW PROGNOZY, NALEŻY ROZWAŻYĆ WŁĄCZENIE DO SCHEMATU LECZENIA bDMARD LUB tsDMARD; W OBECNEJ PRAKTYCE WŁĄCZA SIĘ bDMARD

Dostępne obecnie bDMARD obejmują inhibitory TNF α (adalimumab, certolizumab, etanercept, golimumab i infliksymab), modulatory kostymulacji na limfocyty T (abatacept), inhibitory receptora interleukiny 6 (tocilizumab) a w przyszłości również inne inhibitory receptora IL-6 (sarilumab), inhibitory IL-6 (clazakizumab lub sirukumab), przeciwciała anti-CD20 (wiąże się z limfocytami B) (rituksymab), zarówno w postaci oryginalnych preparatów biologicznych, jak i jako leki biopodobne.

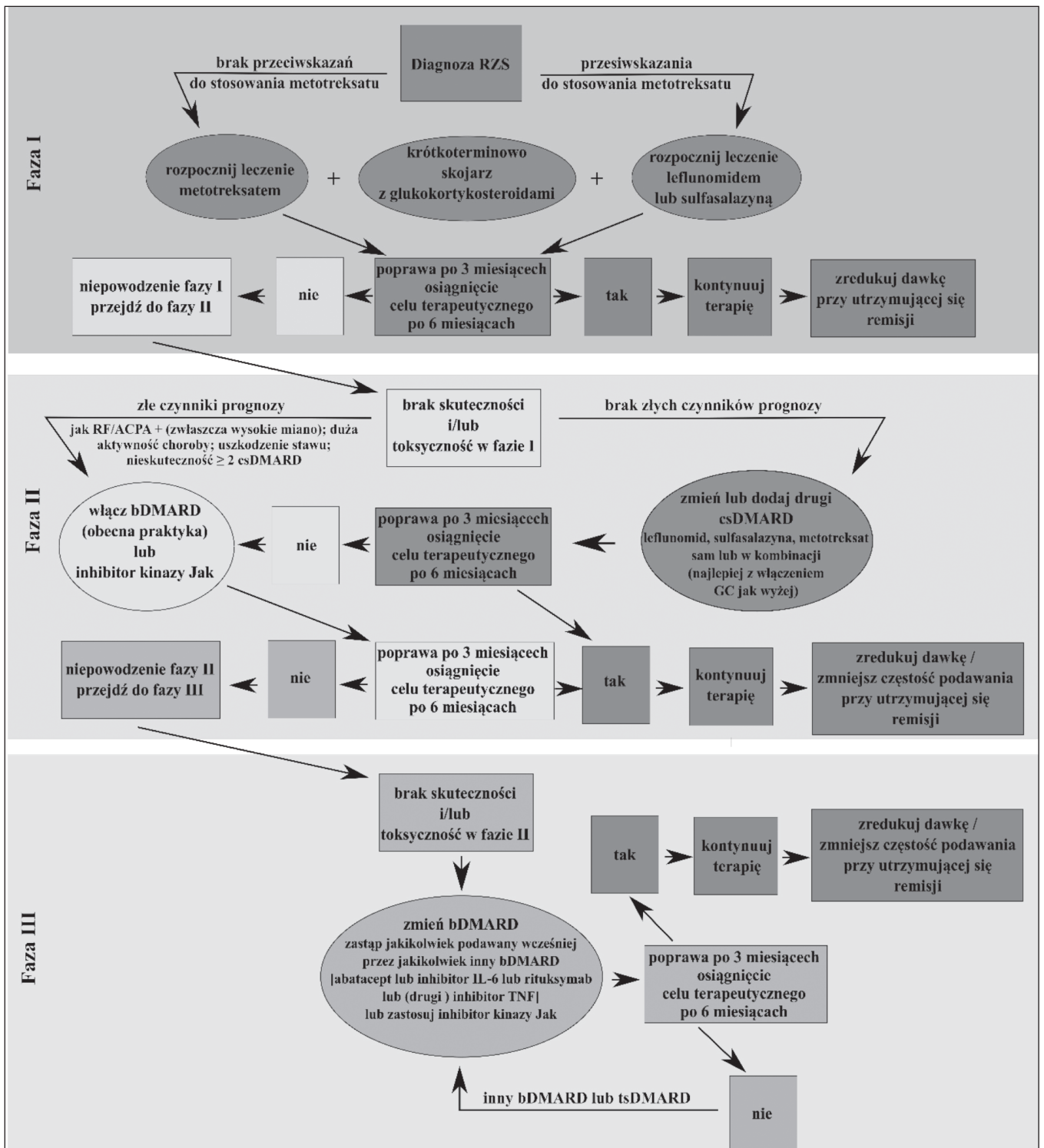
Zalecenia dopuszczają stosowanie tsDMARD, jak inhibitor kinazy Jak (tofacitinib) a w przyszłości inne (baricitinib).

W poprzednich zaleceniach z 2013r użycie tsDMARD zalecano po nieudanym leczeniu bDMARD. Obecnie liczne dane wskazują na dużą skuteczność tsDMARD (baricitinib może być nawet bardziej skuteczny niż inhibitor TNF α). Przewaga boDMARD wynika z większej ilości długofalowych badań, choć zarówno baricitinib, jak i tofacitinib zostały obecnie zatwierdzone w Unii Europejskiej jako leki do stosowania w RZS.

Spośród bDMARD nie wskazano żadnych preferencji co do konkretnych preparatów, co więcej wskazano, że jeśli leki biopodobne mają podobną skuteczność i bezpieczeństwo, to powinny być preferowane ze względów ekonomicznych.

Wykazano dużą skuteczność rituksymabu u pacjentów nieleczonych wcześniej bDMARD i we wczesnym RZS, dlatego jest on często używany w przypadku niewystarczającej odpowiedzi na terapię csDMARD., zwłaszcza jeśli istnieją przeciwwskazania do zastosowania innych bDMARD (chłoniaki w przeszłości lub zaburzenia demielinizacyjne).

Rozważano również ponowne wykorzystanie bDMARD w pierwszej fazie terapii (jak w zaleceniach z 2010 r). wiele badań wskazywało na przewagę terapii skojarzonej nad monoterapią MTX. Jednak wniosek ten nie zyskał większości głosów z uwagi na brak porównania z terapią skojarzoną z GC, a także braku różnicy w ilości niewystarczającej odpowiedzi na leczenie pomiędzy bDMARD + MTX a pacjentami którzy po słabej MTX dostali szybko bDMARD.



Ryc. 1. Algorytm postępowania w terapii RZS.

9. bDMARD I tsDMARD POWINNY BYĆ KOJARZONE Z csDMARD; W PRZYPADKU PACJENTÓW, KTÓRZY NIE MOGĄ STOSOWAĆ CSDMARDS, INHIBITORY SZLAKU IL-6 I tsDMARD MOGĄ BYĆ KORZYSTNIEJSZE W PORÓWNANIU DO bDMARD

Zalecenie to odnosi się do faktu, że wszystkie bDMARD przynoszą lepsze efekty jeśli są skojarzone z MTX niż

w przypadku monoterapii. Wątpliwości wzbudza taka terapia z tocilizumabem i inhibitorami kinazy Jak.

MTX może być stosowany w dawce 7,5–10 mg co poprawia skuteczność inhibitorów TNF. Nietolerancja w przypadku tych małych dawek prowadząca do odstawienia leków jest bardzo rzadka. Również bDMARD mogą być skutecznie łączone z csDMARD.

Poruszono także zagadnienie występowania u pacjentów przeciwciał skierowanych przeciwko podawanym lekom

antyreumatycznym (zwłaszcza w przypadkach braku odpowiedzi na drugi z kolei preparat). Jednak ustalono, że stosowanie MTX w małych dawkach zmniejsza częstość występowania tych przeciwciał. Z kolei w praktyce klinicznej, jeśli występuje dobra odpowiedź na leczenie, obecność takich przeciwciał nie jest przesłanką do zaprzestania terapii.

10. JEŚLI TERAPIA bDMARD LUB tsDMARD OKAŻE SIĘ NIESKUTECZNA, NALEŻY ZASTOSOWAĆ INNY bDMARD LUB WZIĄĆ POD UWAGĘ tsDMARD; JEŚLI TERAPIA INHIBITOREM TNF OKAŻE SIĘ NIESKUTECZNA, MOŻNA ZASTOSOWAĆ INNY INHIBITOR TNF LUB PREPARAT O INNYM MECHANIZMIE DZIAŁANIA

W badaniach wykazano, że zwykle jeśli terapia jednym inhibitorem TNF nie przynosiła rezultatu, możliwe było uzyskanie odpowiedzi pacjenta na inny preparat anti-TNF. Wprawdzie pozostaje tu jeszcze wiele niewiadomych (czy jeden inhibitor kinazy Jak będzie skuteczny jeśli poprzedni lek z tej grupy nie był; czy kolejny inhibitor IL-6 lub jej receptora będzie efektywny w przypadku niepowodzenia leczenia tocilizumabem);

W przypadku gdy drugi (po nieskuteczności poprzedniego) inhibitor TNF nie przyniesie efektu, pacjenci powinni otrzymać preparat o innym mechanizmie działania. Nie powinno się stosować preparatów biopodobnych, jeśli oryginalny (lub inny bsDMARD tej samej molekuly) był nieskuteczny, i na odwrót.

11. JEŚLI PACJENT, PO OGRANICZENIU STOSOWANIA GLIKOKORTYKOSTEROIDÓW, ZNAJDUJE SIĘ W STANIE STAŁEJ REMISJI, MOŻNA ROZWAŻYĆ OGRANICZENIE PRZYJMOWANIA bDMARD, ZWŁASZCZA JEŚLI STOSOWANA JEST TERAPIA W SKOJARZENIU Z csDMARD

Zalecenie to nie uległo zmianie w stosunku do poprzedniej wersji. Termin „zmniejszenie dawki” oznacza zmniejszenie ilości lub częstości podawanego leku. Istotne jest, że Zespół Ekspertów nie sugerował zaprzestania podawania bDMARD po wystąpieniu remisji, gdyż może to prowadzić do ponownego wystąpienia choroby. Jednak w przypadkach, kiedy leczenie zostanie przerwane, a u pacjenta dojdzie do ponownego zaostrzenia się objawów, możliwy jest powrót do pozytywnych efektów po ponownym wdrożeniu leczenia w około 80% przypadków.

12. JEŚLI PACJENT ZNAJDUJE SIĘ W STANIE STAŁEJ REMISJI, MOŻNA ROZWAŻYĆ OGRANICZENIE csDMARD

Ograniczenie to dotyczy zmniejszenia dawki, natomiast całkowite zaprzestanie terapii możliwe jest jedynie w wyjątkowych przypadkach. Wielu reumatologów Grupy Ekspertów jest jednak zdania, że nie powinno się w ogóle zaprzestawać terapii csDMARD.

Obecna aktualizacja zaleceń EULAR została oparta na najnowszych badaniach naukowych i klinicznych i intensywnej dyskusji międzynarodowej Grupy Ekspertów.

Zalecenia te są syntezą podejścia do leczenia RZS przedstawioną w postaci 4 nadrzędnych wytycznych oraz 12 zaleceń. Istotne jest podkreślenie wspólnego podejmowania decyzji, definiowania celu leczenia oraz komunikacji co przekłada się na lepsze przestrzeganie reżimu terapii przez pacjenta. W połączeniu z precyzyjną oceną aktywności choroby i stosowaniem się do ustalonej strategii leczenia powinno zaowocować osiągnięciem celu terapeutycznego u większej, niż dotychczas, liczby pacjentów.

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ADRES DO KORESPONDENCJI

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Nadesłano: 19.10.2017

Zaakceptowano: 20.12.2017

OPISY PRZYPADKÓW
CASE REPORTS**MORPHOLOGICAL AND CRYSTAL CHEMICAL CHARACTERISTIC
OF PANCREATIC LITHIASIS****MORFOLOGICZNA I KRYSTALOCHEMICZNA CHARAKTERYSTYKA
KAMICY PRZEWODÓW TRZUSTKOWYCH****Oleksandr V. Kravets¹, Ihor A. Danilenko², Olga M. Smorodska³, Artem M. Piddubnyi³, Inna-Margaryta S. Zakorko³,
Sergei N. Danilchenko⁴, Roman A. Moskalenko³, Mykola G. Kononenko², Anatolii M. Romaniuk³**¹ DEPARTMENT OF GENERAL SURGERY, SUMY STATE UNIVERSITY, SUMY, UKRAINE² DEPARTMENT OF SURGERY AND ONCOLOGY, SUMY STATE UNIVERSITY, SUMY, UKRAINE³ DEPARTMENT OF PATHOLOGY, SUMY STATE UNIVERSITY, SUMY, UKRAINE⁴ INSTITUTE OF APPLIED PHYSICS OF NATIONAL ACADEMY OF SCIENCE, SUMY, UKRAINE**ABSTRACT**

Introduction: Information on chemical and phase composition of pancreoliths is limited and discrepant. There are reports, that pancreoliths are composed by calcium, phosphate, calcium carbonate or combination of calcium with fatty acids

The aim of the work is studying of structural characteristics of pancreoliths in 5 clinical cases.

Materials and methods: Morphological and crystal-chemical study of five cases of pathological biomineralization in the pancreas were conducted in the work.

Results: Two stones were located in the pancreatic duct, in other cases - in the ductal system of pancreas. Concretion sizes ranged from 0.5 to 1.5 cm in diameter. Pancreatic lithiasis' form depended on the location: in the duct of Wirsung single concretions were found (they were relatively large, oval stones with smooth, regular edges); multiple, small concretions with irregular edges, coral-like stones dominated in the ductal system of pancreas. Histological study of pancreas showed the signs of chronic pancreatitis, tissue fibrosis, atrophy and edema of glandular component, system distension of ducts, nodal mix-cell inflammatory infiltrates, vessels' plethora. Structural phase and chemical analysis of pathological biominerals responded calcite in all studied cases.

Conclusion: The presence of pancreatic lithiasis was found to be accompanied by significant morphological changes of the pancreas. The pancreatolith crystal phase was established to be calcium carbonate in the form of calcite.

KEY WORDS: pancreatic lithiasis, pathological biomineralization, calcite

Wiad Lek 2018, 71, 1 cz. II, 244-248

INTRODUCTION

Pancreatic lithiasis (PL), as a phenomenon of calculus formation in tissue and ductal system of the pancreas, was described by Graef in 1664 for the first time [1]. The majority of current research of PL and pancreoliths are dedicated to the management of this disease and to extracorporeal shockwave lithotripsy (and other methods of stones destruction) [2-9]. The main scientific works, which investigated causes and the mechanism of pancreolith formation, were written in the mid-twentieth century [10, 11]. But since that time the concept of development of pancreas pathology has changed and opportunities of scientific research have increased. This necessitates a complex research of mineral and tissue components of pathological biomineral formations in pancreas.

On average, the incidence of the disease is 0-4 in 1000 among the total world population. This index is known to be 4 per 1000 in the US and Brazil [12].

PL has geographical features related to nutritional fac-

tors. Thus, in developed countries (Western Europe, USA, Japan) PL occurs on the background of alcohol abuse (mostly men aged 30-50 years), on the other hand - in Asia and Africa, in some countries of Latin America PL is associated with chronic malnutrition (mostly women aged 20-30 years) [13].

Etiological factors of PL are not completely understood. They can be divided into several groups: nutritional (alcohol, malnutrition, smoking) [13], chronic inflammation (chronic pancreatitis, autoimmune pancreatitis, bacterial pancreatitis, surgery in pancreatobiliary zone) [5, 12], bile reflex (cholelithiasis and other diseases of biliary system) [12] and genetic factors, which are less common. [14]

The leading mechanism of stone formation is considered to be an increase of pancreas intraductal pressure, which is caused by increased mucin production [15]. In the case of genetically caused PL stone formation occurs with the participation of proteins, which have affinity to calcium [12, 14]. According to other studies data, the mechanism

of stone formation in pancreas is closely concerned with two compounds: stone-forming protein (lithostatin) and fofoferin [16]. Studies data associate additionally stone formation with lactoferin and trypsinogen, but the leading role is still given to stone-forming protein [14, 15].

Information on chemical and phase composition of pancreoliths is limited and discrepant. There are reports, that pancreoliths are composed by calcium, phosphate, calcium carbonate or combination of calcium with fatty acids [10, 11, 15].

THE AIM

The aim of the work is studying of structural characteristics of pancreatoliths in 5 clinical cases.

MATERIALS AND METHODS

Ethics Statement. A written informed consent was obtained from all patients. This research was approved by the Medical Ethics Committee of Sumy Regional Clinical Hospital and Medical Institute of Sumy State University (Protocol No.3/6, 07.06.16).

The surgery material Samples was fixed in 10% formaldehyde in PBS, dehydrated in ethanol, cleared by toluene and embedded in paraffin. Sections of 4 μm thickness were used for staining with hematoxylin-eosin.

The mineral component was isolated by heat treatment at 200 °C for 1 hour. X-ray diffraction studies were performed on the diffractometer DRON4-07 (Burevestnik, Russia). We used CuK_α radiation (wavelength 0.154 nm) under Bragg-Brentano focusing conditions (ϑ - 2ϑ) (2ϑ - Bragg angle). The current and voltage on the X-ray tube were respectively 20 mA and 30 kV. Samples were taken at the continuous recording mode (speed 2 °/min) in the range of 2ϑ angles from 10 to 60°. All processing procedures of experimental data were performed using a licensed software package of experiment supporting and results processing (DIFWIN-1, LLP "Etalon PTTS"). The identification of crystalline phases was carried out by automatically comparing the obtained results with the cards of database Powder Diffraction File 2 without overlaying of restrictions on the elemental composition of the samples; the software package Crystallographica Search-Match (Oxford Cryosystems, www.crystallographica.co.uk) was used in the study.

RESULTS AND DISCUSSION

All cases of PL were represented by male patients. The 1st and the 2nd cases were accidental findings during autopsy studies. In the 3rd, 4th and 5th cases the diagnosis of PL was established at time, operations were conducted. In three cases pancreoliths were found in men, who abused alcohol and / or had cirrhotic liver damage.

CASE 1

The man, aged 45, had a treatment in Surgical Department of Sumy Regional Clinical Hospital in October 2010. The

patient complained about jaundice, itching, ascites, general weakness. He was found to suffer from cholelithiasis . choledochal stone led to obstructive jaundice, which was a reason of performed operations (cholecystectomy, Yurash' choledochoduodenoanastomosis, drainage of abdominal cavity - 07.10.10). The general condition of the patient was complicated by surgery, comorbidities, mixed cirrhosis, diabetes, all that led to cardiac decompensation - acute cardiovascular failure, leading to death. At autopsy pancreas was found to be thick, edematous, to have such size 18,0x2,0x2,5 cm, with areas of fat deposits. In the pancreatic duct the stone was found, it was whitish with smooth rounded edges, in size 0,5x0,8 cm (Fig. 1A).

CASE 2

The 43-year-old man had a treatment in Surgical Department of Sumy Regional Clinical Hospital in January 2013. The patient complained about coffee grounds vomiting, black stool, general weakness, an increase of the abdomen in the volume. Case history: excessive consumption of alcohol for more than 20 years, alcoholic cirrhosis for 8 years. After the examination the diagnosis was established: liver cirrhosis, varicose veins of the esophagus and gastrointestinal bleeding. A conservative therapy (infusion, blood-restoring, blood-substitutive) was performed, which did not give a positive result, the patient died on the first day after hospitalization.

Pathomorphological study of autopsy found, that changes in the liver correspond to mixed cirrhosis, changes in the upper gastrointestinal tract correspond to varicose veins of the esophagus and stomach and to erosive-ulcerative gastritis. At the same time, the pancreas was 12.5x1.5x2.8 cm in size, it was dense, atrophic, with sclerotic changes on a section, yellow, filled by coral white stones 0.4 to 1.5 cm in size, which were located in the ducts (Fig. 1 B).

CASE 3

56-year-old man was hospitalized in Surgery Department of Sumy City Clinical Hospital №5 in December 2016. The patient complained about itching, discoloration of stool, the yellow color of the mucous membranes and skin, general weakness and malaise. From case history: the patient had worsening of chronic pancreatitis several times during past 10 years. Significant worsening of health was observed for last two months. After examination such diseases were diagnosed: chronic recurrent pseudotumorous calculous pancreatitis; Susp Ca of pancreatic head; jaundice, wirsungolithiasis.

Surgical treatment component of that patient was carrying out the surgery: laparotomy, a longitudinal pancreato-jejunosotomy and cholecystojejunostomy on the "excluded by Roux" small bowel loops, drainage of the abdominal cavity. Obtained concretions were 1 cm in a diameter, they had a rough surface, dense texture and shape of duct of Wirsung copy.

The postoperative period passed normal. The patient was discharged from the hospital with recovery.

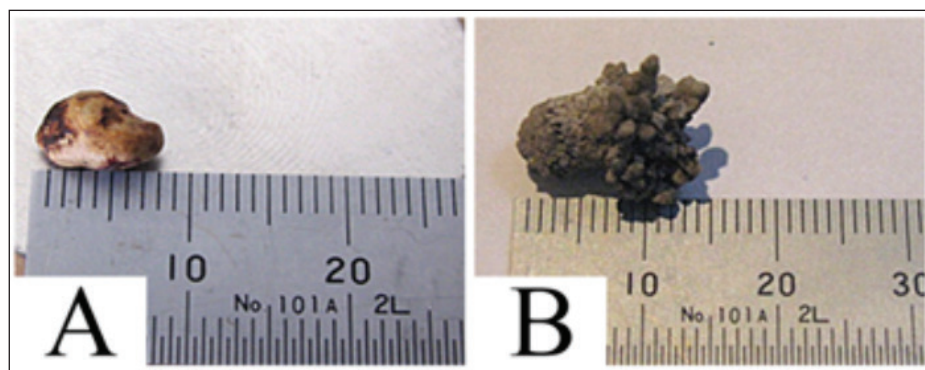
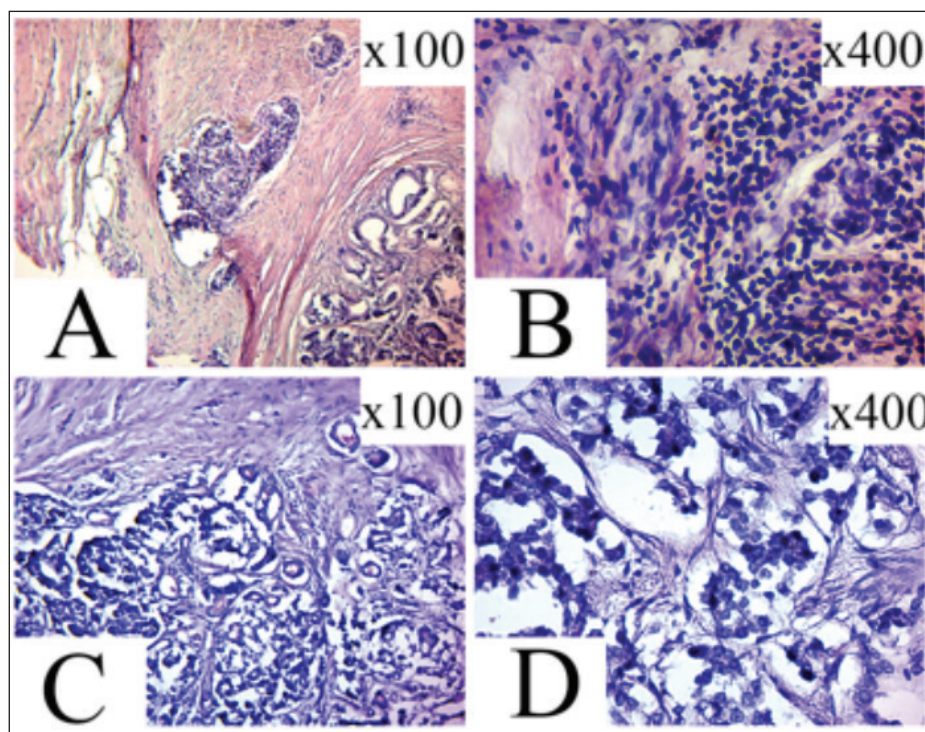


Fig. 1. A. Concretion from the duct of Wirsung of the pancreas (case 1).
B. Coral-like concretion of pancreas ductal system (case 2, after heat treatment).



A. Fibrosis, extension of gland ducts of pancreas, hematoxylin-eosin staining, magnifying x100.
B. Chronic inflammatory infiltration of pancreas tissue, hematoxylin-eosin staining, magnifying x400.
C. Fibrosis, histoarchitectonics abnormality of pancreas, ducts extension with secret remains. PAS – reaction, magnifying x100.
D. Edema and desquamation of glandular epithelium. PAS – reaction, magnifying x400.

Fig.2. Histological examination of the pancreas.

CASE 4

37-year-old man was hospitalized in Sumy City Clinical Hospital №5 in November 2016 with complains about upper abdominal pain radiating to back, general weakness, yellowish color of sclera. Similar symptoms occurred periodically during last 7 years. During examination: the slightly edematous abdomen, yellow color of sclera, slight muscle tension of anterior abdominal wall in the epigastrium and the presence of dense formation (13 cm in a diameter) in the left hypochondrium. After examination such diagnosis was established: chronic calculous pancreatitis, wirsungolithiasis; cyst of the pancreas tail. After stabilizing the patient state surgery was performed: laparotomy, cystojejunostomy and cholecystojejunostomy on the “excluded by Roux“ small bowel loops, drainage of the abdominal cavity. Obtained panreoliths filled densely the duct of Wirsung, almost completely blocking bile and pancreatic juice flow, they had gray-yellow color, dense

texture, irregular shape with a rough surface and, their size was 0.3 cm in a diameter.

The postoperative period passed normal. The patient was discharged from the hospital with recovery.

CASE 5

47-year-old patient was hospitalized in Surgery Department of Sumy City Clinical Hospital №5. He complained about upper abdominal pain, nausea, vomiting, general weakness. From case history: patient was treated for acute and worsening of chronic pancreatitis during last 5 years, occasionally drank hard alcohol, recommended diet was not followed. After examination such diagnosis was established: chronic calculous pancreatitis, wirsungolithiasis. As a result of absence of positive dynamics and the growing lack of exocrine pancreatic function, surgery was performed: laparotomy, longitudinal pan-

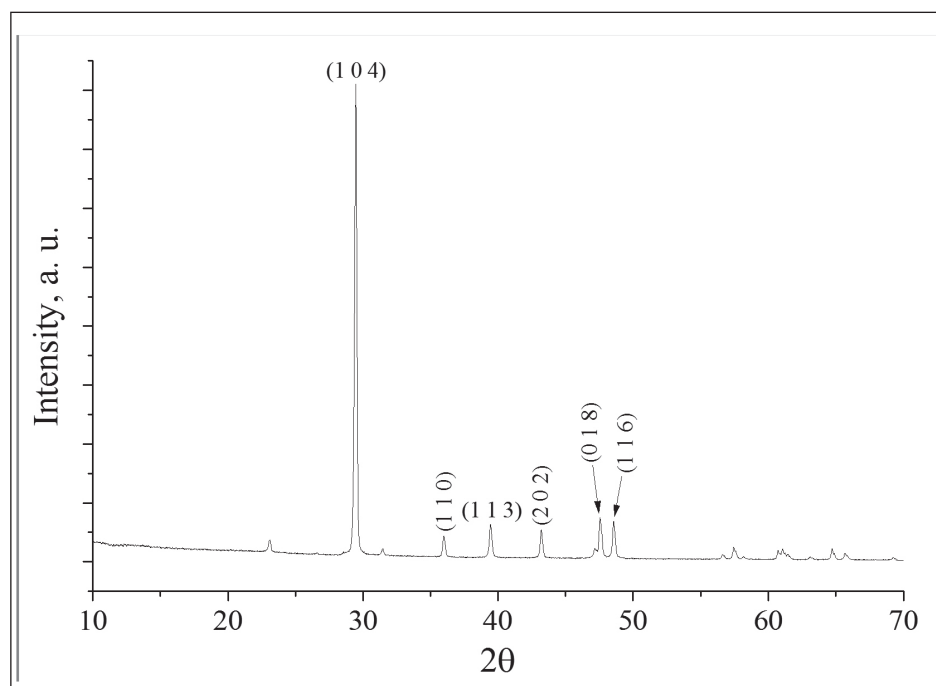


Fig. 3. Original diffraction pattern of mineral material of pancreatic lithiasis

creatojejunostomy, drainage of the abdominal cavity. A significant number of biominerals were found intraoperatively, which were located in the pancreatic ducts. They had a rounded shape, yellow-pink color, dense texture, smooth surface.

Histological examination of pancreas tissues of all clinical cases showed the similar results. Thus, pancreas was characterized by strong development of fibrous tissue, chronic inflammatory infiltration of the stroma and glands (Fig. 2A, B). Significant edematous tissue, histoarchitectonics abnormality, atrophy of glandular system were observed in pancreas with PL in both clinical cases (Fig. 2 C, D). In addition, the extension of pancreatic ductal system was revealed, remains of PAS-positive substance were observed in some duct lumen (Fig. 2 C). Pancreas tissue with pancreatolithes contained focal fat deposits and point hemorrhages.

Research of biomineralith using the methods of applied materials science

The XRD recorded for one of the samples of pancreatic calculi is shown in Fig. 3. By comparing the location of the peaks in the XRD with the JCPDS data on inorganic compounds, the peaks were identified as due to calcium carbonate (CaCO_3) in calcite form. No other phases are observed other than the reported one.

All patients with PL were men aged 43 to 56 years. Three of five patients had a history of alcohol abuse, partly confirming the data literature about negative effects of alcohol on the PL development [13]. Pancreoliths morphology depended on their localization in pancreas: single were detected in the pancreatic duct, they were relatively large, oval stone with a smooth, regular edges; multiple, small concretions with irregular edges, coral-like stones dominated in small ducts and glandular parenchyma of pancreas.

Two stones were located in the pancreatic duct, in other cases - in the ductal system of pancreas. Concretions sizes ranged from 0.5 to 1.5 cm in diameter. Obviously, the shape of biomineral deposits was influenced by their location and local conditions.

Histological examination of pancreas showed the signs of chronic pancreatitis, tissue fibrosis, atrophy and edema of glandular component, system extension of pancreas ducts, focal mix-cell inflammatory infiltrates, vessels' plethora. Of course, chronic inflammation provides the main conditions for pathological biomineralization in pancreas, but the possibility of secondary processes in the surrounding tissues must be remembered, as a response to irritation and injury by stones. Overall, diffuse fibrosis of pancreas, atrophy of glandular parenchyma and chronic inflammation of the gland are the results of PL.

Structural phase of pathological biominerals was represented by calcite in all studied cases. It should be noted, that calcite forms are in a human body only in the inner ear (otolithes, norm) and in gallbladder (some stones, pathology); hydroxyapatite mainly forms in other tissues [17-19]. The main reason of the calcite formation in pancreas tissues is a presence of a great number of bicarbonate ions, which are a defining building material for pancreoliths [20].

Due to the limited number of samples in this study, it was not possible to find a possible connection between the chronic pancreatitis etiology and biomineral depositions [20].

Analysing the clinical results, patients, in whom PL was established in time and surgery was conducted, have recovered. Deaths of patients, in whom PL were accidentally discovered during autopsy, were characterized by severe primary pathology (cirrhosis).

Table. I. Some clinical and pathological characteristics of patients.

Case	Age	Alcohol abuse	Pancreolith localization	Mineral phase	Treatment result
1	43	+	Pancreatic duct	calcite	death
2	45	+	Small ducts	calcite	death
3	56	-	Pancreatic duct	calcite	recovery
4	37	-	Pancreatic duct	calcite	recovery
5	47	+	Small ducts	calcite	recovery

CONCLUSION

Thus, the presence of pancreoliths was found to be accompanied by significant morphological changes in pancreas. Histological examination of pancreas revealed the signs of chronic pancreatitis, fibrosis, atrophy, edema of glandular tissue, system extension of pancreatic ducts, focal mix-cell inflammatory infiltrates, vessels' plethora.

The crystalline phase of pancreoliths is calcium carbonate in the form of calcite.

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Received: 15.10.2017

Accepted: 18.02.2018

OPISTHORCHIASIS AND VIRAL HEPATITIS B: CLINICAL CASES

OPISTORCHOZA I WIRUSOWE ZAPALENIE WĄTROBY TYPU B: PRZYPADKI KLINICZNE

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ABSTRACT

Introduction: Among the cases of biohelminthosis, which are registered in Ukraine, opisthorchiasis is the most common and constitutes the second largest centre in Europe. Due to the growth of migration processes and global tourism, opisthorchiasis is becoming increasingly relevant for the countries of the European Union and the United States. Under modern conditions, the clinical course of many infectious and parasitic diseases has changed.

The aim: The present paper discusses and analyzes the cases of opisthorchiasis and hepatitis B virus which are challenging in terms of diagnostics and choice of treatment tactics.

Conclusion: The course of acute infections, the formation of results and the effectiveness of treatment are influenced by a number of factors, among which mixed infections are of particular interest.

KEY WORDS: opisthorchiasis, hepatitis B, diagnostics, treatment tactics.

Wiad Lek 2018, 71, 1 cz. II, 249-252

INTRODUCTION

Opisthorchiasis is a natural and focal biohelminthosis caused by trematode parasites (*Opistorchis felinus* and *Opistorchis viverrini*). It is characterized by the predominant lesion of the liver, gallbladder, pancreas and has a systemic effect on health, increases susceptibility to other infections, modifies the course of concomitant diseases, and possesses a carcinogenic effect [1,2,3].

The cases of opisthorchiasis caused by *Opistorchis felinus* are registered at the territory of Ukraine and the European Union (EU). The area of its prevalence extends from the Yenisei river basin to the western borders of Europe, however, the disease is focal in nature. The largest focus of opisthorchiasis in the world has been formed in the Ob-Irtysh river basin, where the infection rate reaches 65-95% [1,3,4,5]. In Ukraine, opisthorchiasis is recorded in virtually all regions, but the level of contamination of population by opisthorches, according to different authors, varies from 0.2% to 60.0% depending on the region. The largest endemic focus of opisthorchiasis is the Dnieper river basin – Sumy and Poltava regions [6,7].

Due to the growth of migration processes and global tourism in the world, opisthorchiasis is increasingly registered in the countries where the disease is not endemic [8,9]. As a rule, the contamination with *Opistorchis felinus* occurs due to consumption of infected raw or pickled fish of the carp family during visits to endemic areas or as a result of illicit traffic of this fish from endemic regions [3,9,10]. In addition, the emigration of population from the endemic regions of Ukraine and Russia to the countries of

North America, Western Europe and Israel over the past decades has led to the influx of people with latent chronic opisthorchiasis [3,9,10]. However, health workers from non-endemic regions lack any alertness about this disease, which impedes the timely diagnosis. In addition, the expansion of opisthorchiasis habitat is possible. Interesting is the fact that in Italy from 2003 to 2011 there were 8 outbreaks of acute opisthorchiasis, in which 211 people died. Contamination occurred due to the consumption of raw fish from two lakes in central Italy [11,12,13]. Moreover, the scientific literature of recent years with increasing frequency reports the detection of *Opistorchis felinus* among animals (red fox, ferrets, dogs, cats, fish and mollusks) in Germany, Italy, Poland, Portugal and Spain [3,10,13,14]. The present data indicate the likelihood of circulation of *Opistorchis felinus* in the EU countries in a latent form for many years.

It is generally accepted that clinical manifestations of opisthorchiasis are characterized by non-specificity and polymorphism of symptoms, which complicates the diagnosis [11,12,15]. Meanwhile, the timely detection of the acute phase of the disease is extremely important in terms of prescribing the adequate specific treatment, prevention of chronic process and adverse effects. Certain difficulties also arise in doctor's practice at the stage of verifying the diagnosis of acute opisthorchiasis. This is due to frequent absence of *Opistorchis felinus* eggs in the duodenal content and feces for a long time after contamination. Existing serological diagnostic methods are also insufficiently sensitive and specific, therefore, the detection or absence of specific

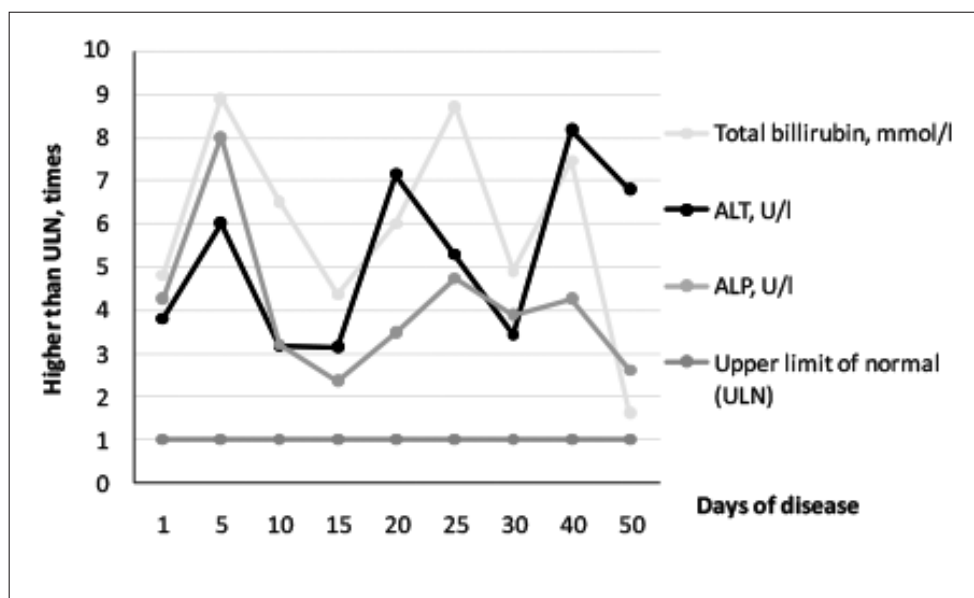


Figure 1. Dynamics of biochemical parameters

antibodies to *Opisthorchis* in the blood is not a valid basis for the diagnosis or its exclusion [10,11,15]. Therefore, the epidemiological history and a set of clinical and laboratory data are crucial in the diagnosis of opisthorchiasis.

Despite the fact that acute opisthorchiasis currently retains typical features [6,7], the presence of concomitant pathology in patients, as well as combined (mixed) infection with the predominant lesion of the hepatobiliary tract complicates the diagnostic search, leads to errors in differential diagnosis and raises difficulties in the choice of treatment tactics. It is known that the presence of opisthorchiasis invasion masks and / or aggravates the course of other pathological processes, and in its turn, the infection that runs with the liver damage, irrespective of their clinical form (manifested or latent), affects the course of opisthorchiasis [2,3,4, 5].

From this point of view, the combination of opisthorchiasis with diffuse liver lesions of viral etiology is particularly relevant, since viral hepatitis B and C constitute an important, socially significant infection both in Ukraine and throughout the world. According to the degree of negative influence on the health of population and the level of morbidity, viral hepatitis in Ukraine occupy a dominant place in the structure of infectious pathology and account for about 30% of all infectious diseases [1].

In connection with the aforesaid, particular attention is given to examples of clinical cases with combination of opisthorchiasis and hepatitis B virus (HBV).

THE AIM

The present paper discusses and analyzes the cases of opisthorchiasis and hepatitis B virus which are challenging in terms of diagnostics and choice of treatment tactics.

RESULTS AND DISCUSSION

CLINICAL CASE 1

A patient, aged 26, a shop assistant at the grocery super-

market, was hospitalized on September 14, 2012 at the infectious diseases clinic for 7 days with the diagnosis of «acute hepatitis A?». At hospitalization: complaints of icterus of the skin and sclera, darkening of the urine, feces discoloration, discomfort in the epigastrium, nausea, repeated vomiting, lack of appetite, general weakness, itching of the skin, temperature rise up to 37.4°C. From the epidemiological history, it was found out that in July 2012, she had rest in Crimea, where during the excursions drank water from mountain sources; 3 weeks before the disease, she ate pickled fish (carp) which was cooked at home. The patient lives in the Orzhytsya district of the Poltava region, which is endemic in opisthorchiasis. Three years ago, the patient underwent a long-term treatment at the dentist's office with teeth extraction and prosthetic care. Physical changes: low-grade fever, jaundice, moderate hepatomegaly. At the additional examination in the clinical blood analysis – leukocytosis ($11.3 \times 10^9/l$), expressed eosinophilia (62%); in the biochemical blood assay – increased bilirubin level ($96 \mu\text{mol/l}$) and transaminases (ALT – 178 U/l, AST – 149 U/l, ALP – 791 U/l); in the ultrasound study of the abdominal cavity – hepatomegaly. In multiple coproovoscopy using formalin-etheral mixture – no eggs of helminths and protozoa were found. In the screening for viral hepatitis A, B and C, as well as HIV – negative results. We diagnosed acute opisthorchiasis and prescribed symptomatic treatment.

Against the background of the conducted treatment (antibiotics, detoxification agents, sorbents, hepatoprotectors), there was a wave-like character of jaundice with repeated clinical and biochemical exacerbations, characterized by the increase in temperature to subfebrile numbers, the increase in dyspeptic and intoxication syndromes, increased level of total bilirubin due to direct fraction, ALT and alkaline phosphatase (Fig. 1).

The hemogram retained leukocytosis ($10.5\text{-}12.6 \times 10^9/l$), eosinophilia (44-67%), in the ultrasound study of the abdominal cavity, the dynamics revealed the signs of

cholecystocholangitis, splenomegaly joined to hepatomegaly. In connection with the wave-like course of jaundice, prolonged increase in transaminases and preservation of low-grade fever, re-examination for viral, autoimmune hepatitis, helminth invasions was conducted, as well as examination for the exclusion of mechanical jaundice and verifying the diagnosis of acute opisthorchiasis. Examination in the dynamics: on the 58th day of the disease, the eggs of *Opistorchis felinus* were found in coproovoscopy; in the PCR study of blood, HBV DNA was detected (1.74×10^4 IU/ml), by ELISA method, serological markers of HBV were found (HBsAg, anti-HBe, anti-HBcor (total) with negative – anti-HBs and HBeAg) and autoimmune (ANA – 1:3200 with negative AMA-2). Final diagnosis: Acute opisthorchiasis against the background of chronic hepatitis B (HBeAg-negative), the replicative phase of moderate activity with autoimmune syndrome.

In view of the prolonged course of the disease, the remitting character of jaundice, preservation of leukocytosis, eosinophilia, high levels of total bilirubin (149.1 mmol/l), ALT (284.7 U/l), alkaline phosphatase (341 U/l), and the presence of autoimmune syndrome, we decided to carry out dehelminthization with praziquantel at a daily dose of 10 mg/kg of the body weight, in combination with detoxification and desensitizing therapy (including glucocorticosteroids). After dehelminthization, the patient's condition improved, within 2 weeks jaundice disappeared, dyspeptic phenomena diminished, body temperature and hemogram rates normalized; however, the increased ALT level remained at 238 U/l, AST – up to 99.6 U/l, ALP – up to 187 U/l.

In January 2013, 3 months after the episode of acute opisthorchiasis, the patient repeatedly presented with complaints of periodic pain in the right hypochondrium, nausea in the morning, itching of the skin. Physical data: subicteric sclera, hepatosplenomegaly. At the additional examination: eosinophilia – 14%, total bilirubin – 34 μ mol/l, ALT – 45 U/l, AST – 32 U/l, ALP – 120 U/l; in the ultrasound study of the abdominal cavity – diffuse changes of the liver, signs of cholecystopancreatitis; the fibroscan data – F0-1 according to METAVIR; in coproovoscopy, the eggs of *Opistorchis felinus* were found. Blood analysis using PCR method revealed HBV DNA (2.5×10^4 IU/ml) in the absence of autoimmune markers (ANA, AMA-2 – negative). The patient was prescribed a repeated course of dehelminthization with praziquantel. After re-treatment within a month, the hemogram and biochemical parameters were completely normalized.

The follow-up study of the patient lasted for three years. During this period, no episode of clinical and biochemical exacerbation of opisthorchiasis was registered. No complaints. At the physical examination – nothing abnormal detected. In the screening for HBV: in blood tests by PCR (12.04.16.) – HBV DNA less than 75 IU/ml, by ELISA method, ANA – not detected, HBsAg, anti-HBe, anti-HBcor (total) are preserved at negative HBeAg and anti-HBsAg; in the ultrasound study of the abdominal cavity – no pathology detected; in the fibroscan data – F0 according to METAVIR.

The given case is of interest because the patient had a mixed pathology of the hepatobiliary system, which determined the peculiarities of the clinical course and laboratory diagnosis of both acute (opisthorchiasis) and chronic (CHB) infectious processes. Thus, acute opisthorchiasis had an atypical wave-like course with increased clinical and laboratory signs of the liver damage, which can be explained by the polyetiologic lesion of the hepatobiliary tract. Attention was attracted by the late verification of the diagnosis of acute opisthorchiasis, as well as the absence of markers of hepatitis B in the acute period of helminth invasion, due to immunosuppressive action of pathogens. For a practitioner, the issue of the timing of dehelminthization in the context of constantly high rates of cytolysis, cholestasis and autoimmune markers turned out to be a challenge. The prescription of praziquantel against the background of detoxification and desensitizing agents with the inclusion of glucocorticosteroids fully justified itself and led to the normalization of clinical and biochemical indicators.

CLINICAL CASE 2

Patient K., aged 26, a manipulation nurse at the ophthalmologic clinic, was hospitalized in June 2016 at the infectious diseases clinic on the 5th day of the disease with complaints of nausea, bitter taste in the mouth, icterus of the skin and sclera, darkening of the urine, weakness. From epidemiological anamnesis: the patient was not vaccinated against hepatitis B; 2 months ago, there was an episode of injury with an injection needle during the intravenous manipulation; the patient regularly undergoes medical examinations for the markers of viral hepatitis B and C, which were identified as negative in January 2016; 3 months ago the patient underwent tooth extraction at the dentist's office. During the last 2 years, she consumes pickled fish from the carp family (home-cooked). Physical data: jaundice, hepatomegaly. At the additional examination: in the complete blood count – neutrophilosis 15%, in biochemical study: total bilirubin 104.1 mmol/l, ALT 736.6 U/ml, AST 1398.1 U/ml, fibrinogen 1.78 g/l, in the ultrasound study of the abdominal organs: moderate hepatosplenomegaly. In the blood test by PCR: HBV DNA – detected, HCV RNA – not detected; serological markers of HBV (HBsAg, anti-HVcor IgM) were detected by the ELISA method.

In coproovoscopy with the use of formalin-etheral mixture – no eggs of helminths and protozoa were found. Clinical diagnosis: Acute hepatitis B, icteric form. Symptomatic treatment (diet, detoxification agents, sorbents) was prescribed. During the week, jaundice intensified, low-grade fever joined, hepatomegaly remained at the same level. At the additional examination: in the complete blood count appeared monocytosis – 21% and eosinophilia – 7%; in the biochemical study – the increased level of general bilirubin up to 181.4 μ mol/l, ALT up to 1791 U/l, AST up to 1001 U/l, ALP up to 242.5 U/l, LDH up to 531 U/l, GGT up to 278.1 U/l. In coproovoscopy, the eggs of *Opistorchis felinus* were found. Final diagnosis: Acute hepatitis B, icteric form against

the background of chronic opisthorchiasis, exacerbation stage. The patient continued the symptomatic treatment until complete normalization of the parameters of cytotoxicity and cholestasis, after which dehelminthization with praziquantel at a daily dose of 10 mg/kg of the body weight was conducted. At the examination of the patient in 6 months, normalization of clinical and laboratory parameters was observed, HBV DNA was not detected by PCR method, seroconversion of HBeAg into anti-HBe, HBsAg into anti-HBs occurred. In the control coproscopy (3-times) and analysis of duodenal contents, no eggs of opisthorchis were found. The follow-up continues.

In this clinical case, attention was attracted by the manifestation of chronic opisthorchiasis against the background of developed clinical presentation of acute hepatitis B. The chronic invasion was detected in a timely manner and dehelminthization in the convalescence period of acute hepatitis B contributed to self-elimination of hepatitis B virus and promoted the patient's recovery.

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Received: 05.10.2017

Accepted: 01.02.2018

PUBLIC HEALTH AND SOCIAL SUPERVISION ISSUES WITHIN PUBLIC ADMINISTRATION OF UKRAINIAN TERRITORIES IN THE LATE 18TH- EARLY 19TH CENTURIES

ZDROWIE PUBLICZNE I KWESTIE NADZORU SPOŁECZNEGO W ADMINISTRACJI PUBLICZNEJ NA TERYTORIUM UKRAINY NA PRZEŁOMIE XVIII I XIX WIEKU

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ABSTRACT

Introduction: The public health system modernization history is based upon the progress in state country administration and administration of healthcare within the sector-wide approach. The WHO European Bureau pays much attention to the National Health Service systems development while implementing their basic policies. The Ukrainian state health service management was founded basing on the regulatory field of the Russian Empire, using the European healthcare promotion experience.

Aim: of the article is the analysis of the regulatory field of police and amenity authorities of the Russian Empire and Ukraine within the medical and social service in the 18th-19th centuries.

Materials and methods: The structure of the article corresponds to the problem city and chronology principles, using the following methods and techniques of scientific learning: the systemic, historic, regulatory comparative, logical and structural-functional analysis of the studied medical-legal phenomena. The study sources are the scientific publications, collections of laws and executive orders of the Russian Empire and Ukraine in the 18th-19th centuries.

Review: As a result of the performed work it can be determined were the main directions of the police competence in late 18th- early 19th centuries.

Conclusion: Preserving health, treatment of the ill and injured, management of medical and social service of those in need, holding various preventive activities and supporting safe environment and regulating the safety of food were the main directions of the police competence in late 18th- early 19th centuries.

KEY WORDS: public health, history of medicine, health management.

Wiad Lek 2018, 71, 1 cz. II, 253-258

INTRODUCTION

The public health system modernization history is based upon the progress in state country administration and administration of healthcare within the sector-wide approach. The WHO European Bureau pays much attention to the National Health Service systems development while implementing their basic policies.

The Ukrainian state-health service management was founded basing on the regulatory field of the Russian Empire, using the European health care promotion experience.

THE AIM

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MATERIALS AND METHODS

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The study sources are the scientific publications, collections of laws and executive orders of the Russian Empire and Ukraine in the 18th-19th centuries.

REVIEW

The modernization of the regional state regulation and medical regulation depended on the state development strategy, stipulated for the perception of state problems by the authorities. During the Russian Empire period of our history, many orders were issued by Catherine the 2nd, which referred to the processes providing for the healthcare management throughout the next decades.

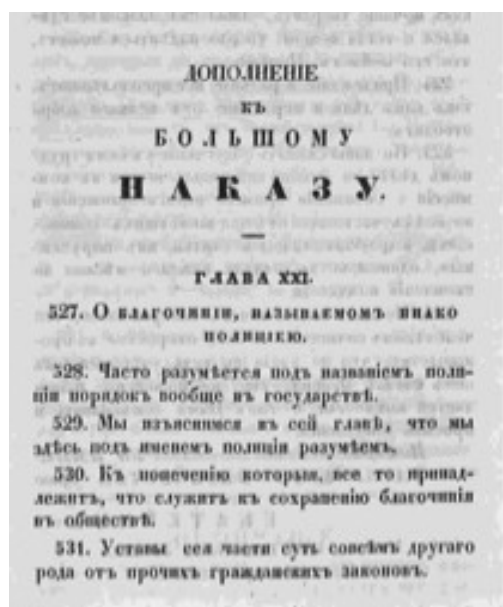


Fig. 1. Tractates of Empress Catherine the 2nd// vol. 1. - 1849. – 666 pp.

The state and medical management were based on the decree “On establishment and management of the governorates of All-Russian Empire”, and the “Great Order” of Russian Empress Catherine the 2nd [1, 2].

According to the documents, the official structural units of the management system were police and amenity authorities.

The terms “police” and “police law” were used not only within the state order context but related to the state or local welfare and the welfare of external country management. Then the police law system (state management system) was subdivided into the “welfare-providing” and “decency-providing” directions [3]. The police law in the late 18th century directly defined that police was a component of state management, protecting the public law, general and personal safety of citizens [4].

In our country the establishment of legal authorities of police within the health service domain was related to the adopted on February the 28th 1768 Addendum to the “Great Order” of Russian Empress Catherine the 2nd, as by this document the “authority of amenity of police forces” was founded.

The Controlling Regulations defined by the Article 554 of Unit XXI state that health refers to the third domain of the police, so the police activities should be aimed at air safety, street and various water sources cleanliness, good quality of food and water provisions, prevention and treatment of diseases, including the infectious ones [2].

Except for the medical aspects, the duties of the police service included various social issues. The article 560 of Unit XXI stipulated for the active police participation in decreasing the share of homeless within the total population. The police were obliged to refer the homeless patients to the treatment institutions and provide for their financial coverage [2].

The “Statute of City Police Department”, approved on 08.04.1782, emphasized social equity [5]. The document clearly states as follows: “The City Police Department cares about all people, without any exception: rich and poor, powerful and outcast ones” (paragraph. 44 of the «Statute»). Paragraph 119 of the “Statute” defines that the police officer must care and seek for those who are in need, making most efforts to provide them with dwelling, food, and work. If the mentioned seems impossible, the duties are delegated to the City Police Department. Paragraph 142 says about the following measures to be taken in cold season to prevent overcooling of people: «In large principal province towns, in each district there must be heating stoves, under shelter, but without high walls, in which one should keep the fire in winter to care about the strangers and night guards». Here, city sergeants received the authority to provide for decent city sanitation conditions. According to paragraph 60 of the “Statute”, “The City Police Department is responsible for clean streets and city quarters during the Cross processions held in religious holidays”, paragraph 140; «The police Department arranges with the master builder for cleaning the streets and disposing of the wastes” and paragraph 139, “controls the master’s activities” [6].

Other functions of the City Police Department included infectious diseases control and monitoring unsafe products trading. Paragraph 232 of the “Statute” says about “prohibition to commit crimes against the general population, which includes: 1) infection dissemination, 2) trading with spoiled food, with the obligatory punishment for these crimes. Part 1 of paragraph 274 disclosed the following: “If a person spreads infection, he should be arrested and sent to the court, where he would be treated appropriately to the Law”, part 2 says: “Should one sell the spoiled food,

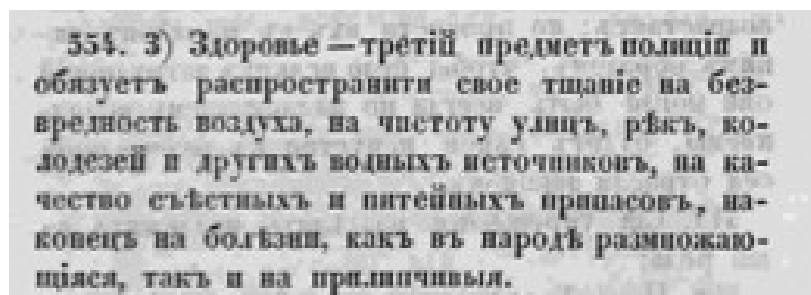


Fig. 2. Tractates of Empress Catherine the 2nd // vol 1. - 1849. – 666 pp.

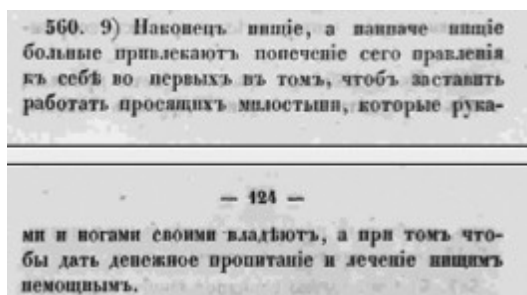


Fig. 3. С Tractates of Empress Catherine the 2nd // vol. 1. - 1849. – 666 pp.



Fig. 4. I.P. Frank 19.03.1745 - 24.04.1821

he will be arrested and treated according to the law” [5].

Another quite curious peculiarity of the “Statute” is that the patient’s hospital expenses were used as a dynamic regional equivalent when detecting certain punitive sanctions. Paragraph 265 states that “Whoever will swear and blaspheme, he will be fined with money equivalent to half-day hospital stay cost, to be kept under arrest until he pays” [5].

So, in late XVIII century, local authorities were represented with police departments or the “City Police Department”, which provided sanitation welfare and social care to the population. So, the Internal Affairs institutions could directly control all vital activity security domains, including quality of food products and water as infectious disease transmission factors [7].

All this predisposed to wide use of the new term “Medical Police”. The competence of medical police comprised



Fig. 5. I.Yu. Veltsin. Outlines of medical amenities or on the people’s health preservation resources depending on the government (1795)

preserving health, treating the sick and injured, management of medical assistance, conducting various preventive actions and supporting safe environment and providing safety of food [4].

This new concept was founded by I.P. Frank. He said: “Medical police is a science of prevention which must guard humans against the harmful consequences of crowded common inhabitation, provide their physical welfare and prolong life term as much as possible”. I.P. Frank is the author of the term “medical police”. He disclosed not only medical personnel’s functions referring to the disease treatment and prevention but explained on the state participation in preventive activities held with all population groups as well as effective control of their conduction. According to I.P. Frank’s concept, the term “medical police” also included responsibility taken by the state for the population health condition. Having considered all the above mentioned, it becomes clear that the term “medical police” is multiple-valued, partially covering sanitation and hygiene, requiring for their regulatory support.

The guide “Outlines of medical amenities or on the people’s health preservation resources depending on the government” (1795), written by I. Yu. Veltsin, states that the authorities must manage population health in order to strengthen the state power through the medical police participation [8].

«Preserving life and health is required for both human functioning and safety and welfare of the state. This is why the Government performs various activities for the safety and welfare of the country. This is why the Government conducts various activities for preserving the health of its citizens. All these activities represent the Medical Police subject. In my opinion, Medical Police is that component

of the State Welfare and Amenity which teaches how, under the supervision and with assistance of the Government, it is possible to preserve the People's health, using various diets and medical bases, and in case of its loss, to restore it», – says the M.F. Rozhdestvenskij's thesis for acquiring the scientific degree of Doctor of Law, termed «Ideas on the governmental actions aimed at preserving life and health of people» (1830) [9]. The issue of the state's responsibility for the public health was covered by his other monographs. "It is within no any other State Welfare domain as the medical police, where the Basic Governance must be present", he stated in his monograph «Bases of State welfare, applied with the Russian laws» [10].

Professor M.F. Rozhdestvenskij thought that all activities held by medical police could be divided into two groups. The first group was represented with activities aimed at eliminating the health and live affecting factors, the second – at restoring the lost health" [10].

Professor M.F. Rozhdestvenskij stated that medical police acted to eliminate or prevent the disease causes. He considered control of the quality of the artificially prepared beverages (wine, vinegar, beer, vodka, etc.) as the main direction of the medical police activity, as last could negatively affect the human health, partially through defect of production, partially through poisonous supplements. He provided for the chemical-analytical control of the production quality before it was released into the sale as well as responsibility for production and trading with the hazardous products. The scientist thought that the hazardous supplements could be detected by severe (without warning) studies of the beverages taken from the shops. If chemical analysis could detect any harmful supplements, both beverages and bottles had to be destroyed, and the person considered guilty had to stand the criminal responsibility [11].

Except for this, medical police performed some other functions. First of all, the medical police concentrated on various factors which predisposed to the health of next generations, even before the child was born. This included management of pregnant women (a pregnant woman received some benefits with refund); if a decision on penalty for committed crime was made, the woman was in advantageous position; there was severe punishment for illegal abortion; decreased workload of the mother of newborns; promotion of public upbringing; promotion of children's physical development by physical exercises; protection of children from poor families from the hard and exhausting work, especially in manufactories.

The second point is that except for the food and beverages, medical police controlled the health of the cattle to be slaughtered as well as the fresh characteristics of meat, fish, vegetables, ready-made dishes and drinks offered to customers; stopped their faking and studied faking methods. This section of duties includes also supplying various territories with water of proper quality.

The third is that the medical police controlled crockery and cutlery quality (first of all – obligatory tinning). The crockery and cutlery made of hazardous compounds, toxic dyes, and poisonous substances were removed from sale.

The fourth point is that medical police functions also included: the explanation of the necessity of and drying swamp regions, performing air humidification in cities and towns, monitoring street cleaning, management of rainwater pipes, regulation of the position of the enterprises, factories and cemeteries to be located far from the city dwelling area.

The fifth point is that the police favored general medical activities aimed at prevention of widespread diseases; informed on newly infected people in the countries where the disease hasn't outbroken yet, introduced marine and ground quarantines [10, 11, 12].

One of the key directions of the medical police activities was the social management: providing the population under quarantine with food and other required provisions. Usually, the government didn't provide financial support of the patients, but in the epidemic, occurrences financing was urgently required to the ordinary support was insufficient, and no one could expect for reliable help from the privates. There the activities aimed at reducing the catastrophe extent had to be taken, though they weren't directly referred as the treatment activities. During infection outbreaks, the city or town experienced lack of vital supplies. To avoid this, the authorities of the quarantined city created the trading commission. To prevent the quarantine-induced raise of prices, socially just charges were established. As trading activities with the quarantined region were abandoned, poor citizens remained without financial support, and the state provided them with the products. There, each adult man and woman could receive a military ration, each child - 50% of the ration, except this, each man, woman, and child received 5 kopecks daily, and each house, if necessary, from 7 to 14 feet of firewood a month [11].

So, the problem of material, medical and auxiliary supplies, required during the infectious outbreaks, was solved by the government. According to the Governmental requirements, pharmacies had to store all the necessary medicines, which the poor population was provided with by prescription.

Another medical-social solution was founding temporary infectious hospitals in the infected areas, which were functioning not only to treat the population but support the homeless, in order to limit the outbreaks.

The other functions performed by the medical police were the organization of medically safe environment: control of various institutions, control of punishments for breaking government and police orders; adopting medical limitations and regulations, and their control. This was reflected in the manuscripts of both medical specialists and lawyers of late 18th –early 19th centuries [10, 12].

In order to provide effective offered measures and some hygienic control conducted not only by medical specialists, and emphasize the importance of police medical activities aimed at preserving public health, the medical police course was introduced into the training of local and city police [4, 13].

The necessity of the organized activity of the state and civil establishments aimed at provision of the environmental safety and public health was noted by Wilgelm Prausnitz: "A private

person can't personally prevent the others from polluting the air she breathes in, prevent the others from polluting the water she consumes, can't prevent the hazards arising before both the community and her own person, caused by crowding. All this refers to obligations of the state health service, the history of which originates in ancient times" [14].

In the mid-18th century the institution which supplied hygienic safety of the city, consisted of the legislative, judicial and administrative power branches. The hygienic legislation performance wasn't a routine process, it required for special knowledge and experience. A sanitation specialist had to perform certain duties and be able to establish the unknown causes and detect the appropriate measures to be held, and control how they were held.

The question of the public health state intervention level was rather complicated, requiring for its management. Some would wish Central Bodies to control whole sanitation issues, records, quarantine cases, building regulations, etc., in the manner similar to that of the state supervisors of railways and telegraphs, which particularly referred to the working hours and salary.

The difference between the central supervision and central administration was significant, the first was aimed at supervising how the others performed their duties, the aim of the second one was to act through the others. The first case stipulated for some independence, while in the last one it was absent [15, 16, 17, 18, 19, 20].

Local sanitation power bodies could hold activities to prevent the diseases locally, being responsible for the unsatisfactory outcome of such activities. It was supposed that the good sanitation administration required for the universal pattern, which could be achieved by the continuous public health supervision by civil sanitation personnel in each region of the country. As for sketching the network of the sanitation institutions, one had to decide what the size of the region was, i.e., what the size of the unit supervised by a certain administration was. Each city would have its own sanitation authority as each city was characterized by a peculiar morbidity cause, the geographic and political city borders defined.

CONCLUSIONS

The predominating in the late 18th - early 19th centuries concept of the State Internal Affairs management, based on the "Statute of City Police Department", which regulated the activities of the police city departments, was aimed at preserving public health within the broad context. The main tasks solved by the state management system, provided for possibilities of medical servicing of all in need, emphasizing medical and social support of the population, during both infectious outbreaks and routine social activities. The main characteristics of the state policy of studied period were similar to the bases of the European policy "Health 2020".

Preserving health, treatment of the ill and injured, management of medical and social service of those in need, holding various preventive activities and supporting the safe environment and regulating safety of food were the main directions of the police competence in late 18th- early 19th centuries.

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Received: 10.09.2017

Accepted: 15.01.2018