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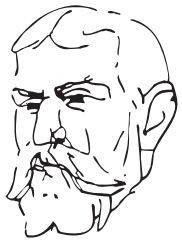

Memory of
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VOLUME LXXIII, ISSUE 9 PART II, SEPTEMBER 2020

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CONTENS

ORIGINAL ARTICLE

REVIEW ARTICLES

CASE STUDIES

VARIA

LETTER TO EDITOR

ORIGINAL ARTICLE

THE MORPHOMETRIC PARAMETERS OF THE PARENCHYMAL AND STROMAL LIVER COMPONENTS OF HEALTHY NEWBORNS FROM HEALTHY MOTHERS WITH A PHYSIOLOGICAL COURSE OF PREGNANCY

DOI: 10.36740/WLek202009201

Sergiy O. Sherstiuk, Stanislav I. Panov, Tetiana I. Liadova, Oleksij I. Tsivenko, Liudmila L. Sherstiuk
V.N. KARAZIN KHARKOV NATIONAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: To determine the morphometric parameters of the parenchymal and stromal liver components of healthy newborns.

Material and methods: The morphometric investigation included 45 liver tissue biopsies of healthy newborns. All morphometric parameters of the parenchymal and stromal liver components were calculated using the Avtandilov microscopic morphometric grid. It was inserted into the microscope ocular tube with a total × 200 microscope magnification. The number of points that were found on the corresponding types of parenchymal and stromal liver components was calculated. In every case, it was selected 10 random microscopic areas and then all data were obtained, calculated and presented as percentages.

Results: Morphometric parameters of hepatocytes: mononuclear hepatocytes – 93.5±7.1 %, two-nuclear hepatocytes – 6.5±1.2 %, BMHC (bi-/mononuclear hepatocytes coefficient) – 0.06±0.01, hepatocytes with fat vacuoles – 0.5±0.2 %. Parenchymal and stromal liver components: parenchyma – 74.2±4.3 %, stroma (including blood vessels and bile ducts) – 25.8±2.6 %, SPI (stroma/parenchyma index) – 0.34±0.01. Morphometric parameters of all of the liver components: hepatocytes – 74.2±4.3 %, portal tracts – 3.1±0.6 %, central veins – 9.3±1.4 %, sinusoids – 10.5±1.3 %, bile ducts – 2.9±0.2 %. Expression level parameters: fibronectin – 17.3±2.5 %, collagen type I – 9.7±1.9 %, collagen type III – 10.1±0.9 %, collagen type IV – 5.9±0.2 %. Parameters of liver fibrosis biomarkers: APRI (index) – 0.19±0.01, a FIB-4 (index) – 0.022±0.001.

Conclusions: The morphometric parameters of the parenchymal and stromal liver components of healthy newborns can be used as a control group in the study of any pathological conditions of the liver of newborns.

KEY WORDS: liver, newborn, liver parenchyma, liver stroma

Wiad Lek. 2020;73(9 p. II):1895-1899

INTRODUCTION

Unfortunately, timely diagnosis of liver disease in newborn infants remains an urgent problem today, since various disorders of the liver often have virtually the same initial clinical features, or they generally have a latent course. Since liver dysfunction is progressive, early detection of pathology allows time to initiate appropriate therapeutic measures and significantly improve the prognosis [1]. The role of the pathomorphologist in addressing common problems of liver disease in children is likely to change in the future with the progresses of molecular genetic revolution. However, even when biochemical, microbiological, and immunological laboratories already provide essential diagnostic information, an informed morphological interpretation of liver disease in children continues to be an important method of diagnosis [2]. Primary interpretation of liver disease in children may occur through clinical and laboratory data, but differential diagnosis and prognosis of liver disease require more accurate morphological data, and this primarily concerns the assessment of the stromal-parenchymal component of the liver [3]. In order to correctly and reliably evaluate the quality of the stromal-parenchymatous component of the liver of a newborn baby and to correctly interpret the presence or absence of liver pathology, information on the normal rates of stroma and liver parenchyma in healthy newborn infants should be compared. The study of world and national resourses showed the absence of such data, so there is a need to provide such information to the scientific community and practitioners to optimize diagnosis of liver disease in children.

THE AIM

Study of morphometric parameters of stromal-parenchymatous component of liver of healthy full-term newborns from healthy mothers with physiological course of pregnancy, with further provision of the obtained data to the scientific community and practitioners to optimize the process of diagnosis of liver pathology in children.

MATERIALS AND METHODS

Investigated 45 biopsies of the liver tissue of healthy term infants of 37-40 weeks gestational age born to healthy

mothers with physiological pregnancy and died due to severe head injury, or premature detachment of normally situated placenta during delivery; life expectancy in all cases did not exceed 24 hours. The autopsiy material research was conducted according to the requirements of «Instruction on conducting autopsies» (Ministry of Health of Ukraine order № 6 from 17.01.1995); the requirements, norms and standard provisions on ethics of the Ministry of Health of Ukraine № 690 from 23.09.2009 p.; «The procedure for the removal of biological objects from the dead, whose bodies are subject to forensic and pathoanatomical research, for scientific purposes» (2018). The material was collected during the period from 2010 to 2018 in pathoanatomical department of Kharkiv Regional Perinatal Center.

For morphological study liver slices were fixed in 10% solution of neutral formalin and then subjected to standard processing through liquid Nikiforov (96% alcohol and diethyl ether in the ratio 1: 1), chloroform and then paraffinization.

The recived blocks were sliced intro pieces of 4–5 μm thick by Microm HM - 340 microtome. The obtained samples were coloured with hematoxylin and eosin as well as using method Mallory.

Regenerative activity of liver parenchyma was evaluated by the number of binucleated and mononucleated hepatocytes. The number of binucleated / mononucleated hepatocytes was calculated using the Avtandilov microscopic morphometric grid, which consisted of 100 equidistant points and was inserted into the microscope eyepiece with × 200 magnification of the microscope. The number of dots that occurred in single and dual hepatocytes was counted. Each sample was studied in 10 randomly selected fields of view, and the data were calculated and presented as a percentage [4]. Also, the calculated rate of binucleated / mononucleated hepatocytes (RBMH) by the formula:

RBMH = Number Of Binuclear Hepatocytes (%) / Number Of Mononuclear Hepatocytes (%)

For morphometric assessment of the stromal, parenchymatous, vascular and biliary components of the liver, was also used Avtandilov microscopic morphometric grid, which consisted of 100 equidistant points and was inserted into the microscope eyepiece with × 200 magnification of the microscope. The number of points that fell on the stromal (portal tracts, septa), parenchymatous (hepatocytes), vascular (portal vessels, central veins, sinusoids) and biliary (bile ducts) components of the liver were calculated. Each sample was examined in 10 randomly selected fields of view, and then the data obtained were calculated and presented as a percentage. Also, stromal-parenchymal index (SPI) was calculated by the formula:

SPI = Stromal Index / Parenchymal Index

Immunohistochemical features of the components of the liver were studied using indirect immunoperoxidase method on paraffinized sample of 3-5 microns thick. In all cases, each sample was studied in 10 randomly selected fields of view, and positive signals (positive expression in the form of a brown color) were measured by Avtandylov microscopic morphometric grid, which consisted of 100 equally equidistant points was inserted into the eyepiece eyepiece with × 200 magnification of the microscope. The number of dots that occurred in the positive signal was counted, and the data were calculated and presented as a percentage. The samples were studied using a BX43 optical microscope (Olympus Corporation, Tokyo, Japan) and the expression was analyzed using a quantitative image analysis system (Image-Pro Plus 6.0; Media Cybernetics Inc., Rockville, MD, USA).

Fibronectin expression level fibronectins antibodies (mouse polyclonal; 1: 100; sc-8422; Santa Cruz Biotechnology, Inc.) were usied. The blocks were heated for 60 minutes at 60 ° C, deparaffinized with xylene and washed in alcohols with a decrease in their concentration. Antigens were obtained with citrate buffer (pH 6.0) in a microwave oven for 5 minutes. After being processed in 1.5% H_2O2 at 37 ° C for 30 minutes to block endogenous peroxidase activity, the samples were incubated with primary antibodies overnight at 4 ° C and then incubated with secondary antibodies (PV-9002; OriGene Technologies, Inc., Beijing, China) for 30 minutes at room temperature. Finally, samples were couloured using diaminobenzidine followed by hematoxylin contrast.

To assess the level of expression of collagen types I and III collagen using antibodies against type I and III (polyclonal rabbits, 1: 600; Abcam, Cambridge, UK). The blocks were heated for 60 minutes at 60 ° C, deparaffinized with xylene and washed in alcohols with decreasing concentration. The preparations were first pre-incubated in 3% H2O2 solution for 10 minutes at room temperature to block endogenous peroxidase activity, and then the antigen was extracted with citrate buffer (pH 6.0) in a microwave oven at 95-98 ° C for 12 minutes, followed by incubation for 5 minutes at room temperature to block non-specific background staining. Then, incubated at room temperature for 30 minutes with primary rabbit polyclonal antibodies against type I and III collagen. The obtained preparations were washed four times with buffer, treated with streptavidin, peroxidase and chromogen DAB. Finally, the sections were stained using diaminobenzidine followed by hematoxylin contrast.

To assess the level of expression of type IV collagen used antibodies against type IV collagen (polyclonal mice; 1: 100; Leica Biosystems, Newcastle, UK: PHM-12, UK). The blocks were heated for 60 minutes at 60 ° C, deparaffinized with xylene and washed in alcohols with decreasing concentration. Antigens were obtained with citrate buffer (pH 6.0) in a microwave oven for 5 minutes and then cooled at room temperature for 20 minutes. After processing 3% solution of H2O2 at 37 ° C for 30 minutes to block the endogenous activity of peroxidase, sections were incubated with primary antibodies overnight at 4 ° C, and then incubated with secondary antibody (K-ASSAY Collagen Type IV Staining Kit, Kamiya Biomedical Company, USA) for 30 minutes at room temperature. Finally, sections were stained using diaminobenzidine followed by hematoxylin contrast.

To assess the presence of liver fibrosis, a non-invasive analysis of two biomarkers of liver fibrosis in blood APRI and FIB-4 was performed. Indicators of biomarkers of fibrosis were calculated according to officially published

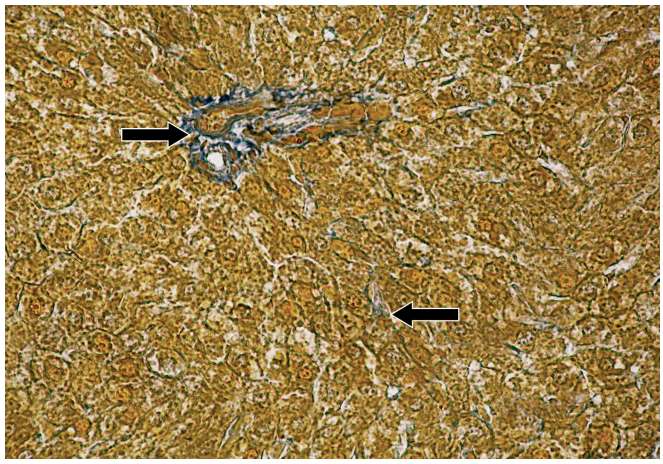

Fig. 1. The liver of a healthy newborn baby. Conventional histoarchitectonics of the liver, normal development of the stromal component (arrows). Mallory coloring. × 200.

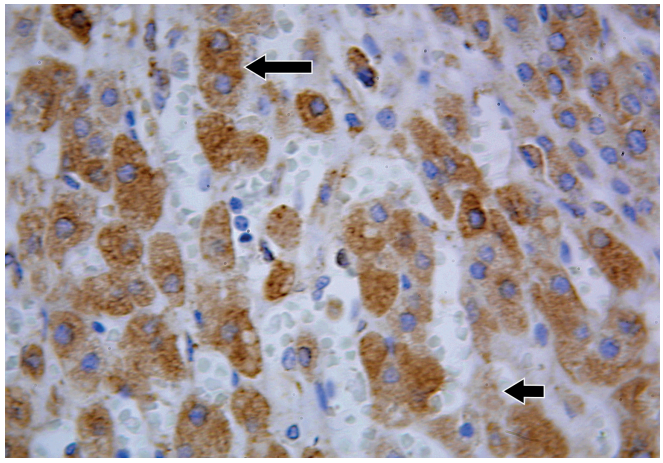

Fig. 2. The liver of a healthy newborn baby. Fibronectin matrix protein in the cytoplasm of hepatocytes (long arrow) and in Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method. ×400.

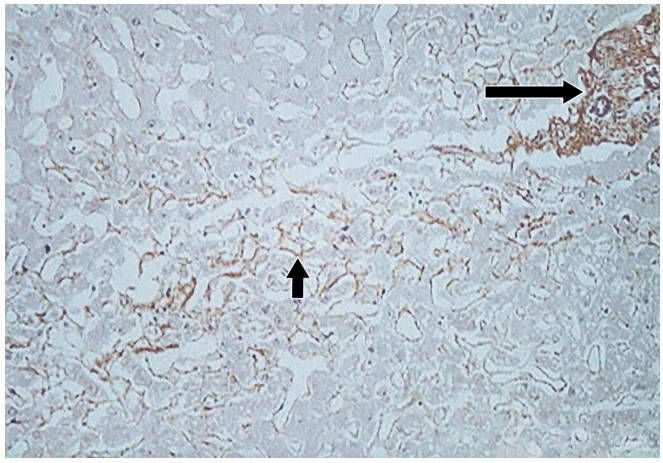

Fig. 3. The liver of a healthy newborn baby. Expression of type I collagen in the stroma of the portal tracts (long arrow) and in the Disse spaces along sinusoids (short arrow). Indirect immunoperoxidase method. × 200.

recommendations [5, 6, 7, 8] using the following formulas:

APRI = [AST (IU/L) / AST (ULN) (IU/L)/ Platelet Count (10^9/L)] × 100, (1)

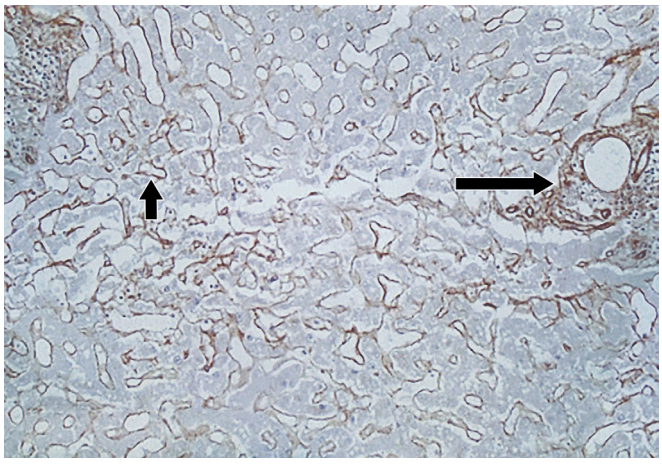

Fig. 4. The liver of a healthy newborn baby. Expression of type III collagen in the stroma of portal tracts (long arrow) and in Disse spaces along sinusoids (short arrow). Indirect immunoperoxidase method. × 200.

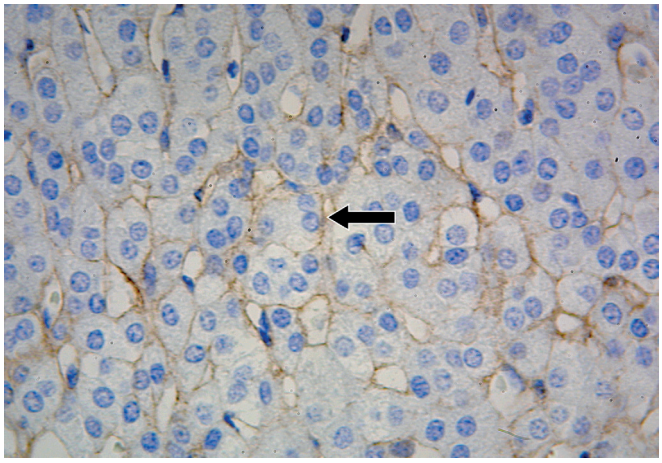

Fig. 5. The liver of a healthy newborn baby. Expression of type IV collagen in Disse spaces along sinusoids (arrow). Indirect immunoperoxidase method. × 400.

AST – aspartate aminotransferase; AST ULN (Upper Limit of Normal) – aspartate aminotransferase (40 IU/L).

FIB-4 = [Age (years) × AST (IU/L)] / [Platelet Count (10^9/L) × √ ALT (IU/L)] (2)

ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Statistical processing of the results was performed using the standard statistical software package «STATISTICA 10.0» and «MS Excel». For derived indicators calculated arithmetic mean (M), the average standard error (m). To assess the degree of reliability of differences between groups using U-criterion Mann-Whitney.

RESULTS

In the macroscopic study liver was elastic to the touch and had excellent thin translucent capsule. On the cross section of the liver tissue was red-brown, homogeneous, with properly developed and unevenly full-blooded hepatic veins. Microscopically was observed the normal radiarna-beam structure, normal sinusoids and central veins, and a few small sites of extramedullary hematopoiesis.

Hepatocytes had slightly granular eosinophilic cytoplasm and round basophilic nucleus. The morphometric parameters of hepatocytes were as follows: mononuclear hepatocytes - 93.5 ± 7.1%, binuclear hepatocytes - 6.5 ± 1.2%, RBMH (binuclear / mononuclear hepatocytes coefficient) - 0.06 ± 0.01, hepatocytes with fat vacuoles - 0.5 ± 0.2%.

The portal stroma was developed normally and consisted with collagen fibers.

Stromal-parenchymal indices of liver were as follows: parenchyma - 74.2 ± 4.3%, stroma (including vessels and bile ducts) - 25.8 ± 2.6%, SPI (stromal-parenchymal index) - 0.34 ± 0.01.

The morphometric parameters of all components of the liver were as follows: hepatocytes - 74.2 ± 4.3%, portal tracts - 3.1 ± 0.6%, central veins - 9.3 ± 1.4%, sinusoids - 10.5 ± 1.3%, bile ducts - 2.9 ± 0.2%. Across the liver parenchyma had a moderate amount of fibronectin matrix protein in the cytoplasm of hepatocytes and in the Disse spaces along of sinusoids.

Tape I and III had moderate expression in the stroma of the portal tracts. Also, those types of collagen were detected in Disse spaces along of sinusoids in a small amount, which was documented by their weak expression.

There was a moderate amount of type IV collagen in the Disse spaces along sinusoids, which is normal major component of basal membranes.

The levels of expression of fibronectin, type I, III and IV collagens in the stromal component of the liver were as follows: fibronectin - 17.3 ± 2.5%, type I collagen - 9.7 ± 1.9%, type III collagen - 10.1 ± 0.9%, type IV collagen - 5.9 ± 0.2%.

The level of ALT in the blood of newborns averaged 12.6 ± 2.2 IU/L, AST - 21.2 ± 2.7 IU/L, platelets - 267.3 ± 22.6 × 10^9/L. The biomarkers of liver fibrosis were as follows: APRI (index) - 0.19 ± 0.01, and FIB-4 (index) - 0.022 ± 0.001.

DISCUSSION

The world literature is lock of any studies about morphometric parameters of the stromal-parenchymal components of healthy liver of healthy infants from mothers with physiological pregnancy. The resulting morphometric data stromal-parenchymatous component of a normal liver (morphometric parameters of the number of hepatocytes, portal tracts and central veins, sinusoids, bile ducts, fibronectin, collagen I, III and IV types) can be used as control group in the study of variour pathological conditions of the liver of newborn children.

Liver biopsy is considered the «gold standard» for assessing the presence and severity of fatty liver and especially liver fibrosis. However, this procedure is invasive and is intended for children only in extreme cases [9]. Therefore, the scientific community has proposed two serum biomarkers APRI and FIB-4, which can reliably detect the presence and severity of liver fibrosis without the need for a traumatic liver biopsy procedure [10]. APRI and FIB-4 liver fibrosis biomarkers are simple and easy to use, and there are no complex components in formulas that requireds to calculate them. To calculate both biomarkers of fibrosis, it is necessary to register the ALT, AST, and platelet counts in the blood plasma (routine total blood count and hepatic metabolic panel), and for the FIB-4 biomarker, one must have the information about patient's age.

Biomarkers of liver fibrosis have been well studied in adults, however, there are lock of any studies about biomarkers of liver fibrosis in healthy newborns from healthy mothers with physiological pregnancy, so this study presents the data about APRI and FIB-4 for the first time.

CONCLUSIONS

The presented morphometric data of stromal-parenchymal component of the normal liver of healthy infants from healthy mothers with physiological pregnancy (morphometric parameters of number of hepatocytes, portal tracts and central veins, sinusoids, bile ducts, fibronectin, collagen I, III and IV types), and biomarkers of liver fibrosis APRI and FIB-4 can be used as a control group in the study of any pathological conditions in the liver of newborns.

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This work is a fragment of a comprehensive research program of the Human Anatomy Department of the V.N. Karazin Kharkiv National University: "The impact of maternal pathology on the fetal and newborn organism development". State Registration Number: 0117U004838. This work was funded according to the plan of that program. The authors did not receive any financial support from the manufacturers of medical instruments and drugs.

ORCID and contributionship.
Sergey O. Sherstiuk: 0000-0001-6062-7962 [A,E,F]
Stanislav I. Panov: 0000-0001-9264-0088 [B,C,D]
Tetiana I. Liadova: 0000-0002-5892-2599 [B,C,E]
Oleksij I. Tsivenko: 0000-0003-0839-9768 [B,C,E]
Liudmila L. Sherstiuk: 0000-0002-2993-2843 [B,C,E]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Stanislav I. Panov
V. N. Karazin Kharkiv National University
6 Svobody Sq., 61022 Kharkiv, Ukraine
tel:+38 099 460-39-94,
e-mail: StanislavPanov@karazin.ua

Received: 22.09.2019
Accepted: 17.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

EXAMINING THE ROLE OF THE NITRIC OXID SYSTEM AS THE ESSENTIAL PATHOGENETIC LINK IN STEVENS-JOHNSON SYNDROME

DOI: 10.36740/WLek202009202

Natalya V. Ivanyushko – Nazarko, Orysya O. Syzon, Svitlana V. Volbyn, Tetyana I. Rudnyk, Marianna O. Dashko
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

The aim: To determine a possible role of nitric oxide system as one of the pathogenesis links in Stevens-Johnson syndrome depending on the severity of disease progression.

Material and methods: We examined 11 patients with Stevens-Johnson syndrome. The function of nitric oxide system (NO - NOS) in blood serum was examined.

Results: During the study of nitric oxide system (NO-NOS) in patients with SJS, it was observed that NO_2^- level was increased by 1.53 times, NO_3^- level – by 3.33 times, activity of total NOS – by 5.78 times, constitutive (cNOS) – by 1.81 times and inducible (iNOS) – by 13.36 times.

Conclusions: The intensity of nitric oxide system function was studied in patients with Stevens-Johnson syndrome and dependence of changes of its parameters from the clinical signs of disease was detected. It was found that the determination of nitrite and nitrate anion levels in blood serum can be used for the purpose of predicting the disease course and choosing the therapy methods for the patients with SJS.

KEY WORDS: allergy, medications, Stevens-Johnson syndrome, nitric oxide system

Wiad Lek. 2020;73(9 p. II):1900-1903

INTRODUCTION

More and more frequently, the diseases that constitute a group of severe toxic and allergic skin conditions, Stevens-Johnson syndrome (SJS), are diagnosed by dermatovenerologists in their everyday practice [1]. An increased incidence of diseases of this nosology is the result of the increase in the number of medications available in the pharmaceutical market, which leads to mass self-medication of population [2]. Today patients tend to seek medical treatment after self-medication, when they have already taken medicines of different pharmacological groups, and thus doctors observe either sustained form of dermatosis or development of drug allergy.

Drug allergy can also be triggered by conditions associated with the effect of adverse environmental factors on the body, genetic predisposition, general allergization of the body, unsafe work environment, chronic diseases, etc. as well as often unjustified prescription of multiple medicines taken simultaneously when conducting complex medicamentous therapy [3,4,5].

Drug allergy clinical signs may include [6]: hives, angioedema, unclassified exanthems, fixed drug eruption, drug-induced vasculitis, erythema multiforme (at moderate allergy symptoms), anaphylactic shock, Stevens-Johnson syndrome and Lyell's syndrome or toxic epidermal necrolysis (at severe drug allergy symptoms) [2,7].

Stevens-Johnson syndrome is a severe toxic and allergic skin reaction, often fatal, which is characterized by acute onset, fever, bullous eruption and large blisters on the swollen and hyperemic mucous membrane of the oral cavity, pharynx, tongue, tonsils, gums, which later burst, merge and get grey coating. Apart from the mucous membrane, which is predominantly affected in SJS, erythematous, vesicular and papular eruption appears on the face, torso and limbs [8,9]. The following degrees of severity in the course of SJS are distinguished: mild (mild lesion of oral mucosa, single erythematous eruption on the torso and limbs), moderate (low-grade fever, lesion of oral mucosa, small blisters on erythematous background) and severe (fever, lesion of mucous membranes of both mouth and reproductive organs, massive bullous eruption on erythematous background, skin lesion up to 10%). In 50% of cases, SJS is triggered by medicines, in other cases it is caused by the infectious agents etc. [10,11]. SJS pathogenesis has not been fully studied. The disease is considered as a hyperergic reaction, which affects keratinocytes and is triggered by infection, medications and toxic agents [12,13]. The effect on keratinocytes can be conditioned by all four types of inflammation according to immune system classification, however the most significant are of the 3-4th types. The mortality rate in SJS is from 5 to 10% of the cases [14,15].

Nitric oxide (NO), which is synthesized in the body, is a unique intra- and extracellular messenger that mediates neurotransmission, cell cooperation, vasodilation, immune response, etc. The synthesis of NO from L-Arginine is carried out by three main NOS isoforms, in particular: two constitutive synthases (cNOS) (neuronal and endothelial) and one inducible NO synthase (iNOS). An increased or

Table I. $NO2^-$, $NO3^-$ content, NO synthases activity (M±m) in the blood serum of patients with Stevens-Johnson syndrome

Indicator, µmol/l	Patients with SJS, n=11	Control group, n=20
NO_2^-, µmol/l	6.82±0.41*	4.45±0.19
NO_3^-, µmol/l	10.93±1.14*	3.28±0.14
NO_2^-/NO_3^-	0.62±0.05*	1.36±0.07
Total NOS, nmol/min·l	1.85±0.25**	0.32±0,05
cNOS, nmol/min·l	0.38±0.07*	0,21±0.03
iNOS, nmol/min·l	1.47±0.19**	0.11±0.02
cNOS/iNOS	0.26±0.05**	1.91±0.22

Note: Significant difference between the indicators in patients and control group individuals by $p<0.05$ – *, $p<0.01$ – **.

Table II. $NO2^-$, $NO3^-$ content, NO synthases activity (M±m) in the blood serum of patients depending on Stevens-Johnson syndrome severity

Indicator	Patients with different SJS severity	
	mild and moderate, n=6	severe, n=5
NO_2^-, µmol/l	7.46±0.52**	5.59±0.37
NO_3^-, µmol/l	8.38±1.03*	12.06±1.25**
NO_2^-/NO_3^-	0.89±0.07*	0.46±0.03**
Total NOS, nmol/min·l	1.49±0.14**	2.09±0.28**
cNOS, nmol/min·l	0.33±0.05	0.39±0.08*
iNOS, nmol/min·l	1.16±0.10**	1.70±0.21**
cNOS/iNOS	0.28±0.06**	0.23±0.03**

Note: Significant difference between the indicators in patients and control group individuals by $p<0.05$ – *, $p<0.01$ – **.

decreased production of NO and its metabolites in the body is one of the factors of the regulation of physiological functions as well as pathogenesis of pathological conditions [16].

Both an insufficient and excessive production of NO triggers pathophysiological reactions, which are formed in tissues and play a significant role in pathogenesis of different inflammatory conditions, arterial hypertension, pulmonary hypertension, diabetic angiopathy, thrombosis, as well as skin conditions, neurological and digestive disorders, etc. [17]. An excessive NO production due to NOS induction is an important factor of general and local hemodynamic and other disorders. The activation of NO synthesis is typical of shocks of different nature - heat, septic, cardiogenic, anaphylactic and hemorrhagic ones. Deficiency of NO, which is connected with its insufficient production and accelerated decomposition, determines disadaptation to hypoxia of different nature, immunopathological reactions and endothelial dysfunction [18,19].

A wide spectrum of bioregulatory effect of NO, in particular, its involvement in the course of allergic inflammation (cytotoxic, immune complex-mediated reactions), regulation of vascular tone and coagulation, cell proliferation, etc., suggests an involvement of NO in SJS pathogenesis and allows for a study of the condition of NO - NOS system in patients, taking into consideration lack of information on this issue in the available literature sources.

THE AIM

The aim of our study was to define a possible role of nitric oxide system as one of the pathogenesis links in Stevens-Johnson syndrome by determining the content of stable metabolites of nitrite and nitrate anions, constitutive (cNOS) and inducible NOS (iNOS) in the blood serum of patients in case monitoring.

MATERIAL AND METHODS

We examined 11 patients with Stevens-Johnson syndrome (range 30-49 years, 6 men and 5 women). The levels of the disease severity were different in the patients under examination (mild and moderate in 6 individuals and severe in 5 individuals). A control group consisted of 20 apparently healthy individuals.

The analysis of the NO - NOS system function was made in the blood serum of 11 patients with SJS. The concentration of nitrate anion (NO_2^-) was measured by spectrophotometric method using a standard Griess reagent [20]. The level of nitrate anion (NO_3^-) was determined by means of brucine reagent [21].

The activity of total NOS (Ca^{2+} dependent and Ca^{2+} independent) was studied by using a classical method adjusted to the spectrophotometric measurement of one of the reaction products - nitrite anion [22]. Total NOS was examined first and then Ca^{2+} independent iNOS (by adding EDTA) was measured. The content of cNOS was calculated by subtracting iNOS concentration from the level of total NOS.

RESULTS AND DISCUSSION

The bioregulatory effect of NO, its involvement in the course of allergic inflammation, regulation of vascular tone and coagulation, cell proliferation, etc., suggests an involvement of NO in SJS pathogenesis [16,17,18,23,24].

A significant increase in the level of nitrite anions ($p<0.05$) and nitrate anions ($p<0.01$) was found in the blood serum of patients with SJS, at that, their ratio was sharply decreasing ($p<0.01$) compared to the similar parameters in healthy individuals (Table I). The activity of total NOS as well as constitutive and inducible forms significantly exceeded the same in the control group individuals, and the activity of iNOS was especially increasing in SJS ($p<0.01$). The cNOS/iNOS ratio in patients proved to be significantly lower in comparison with the control group ($p<0.01$).

A significant increase in NO_2^- and NO_3^- content and in total and INOS activity was observed at mild and moderate severity of SJS, whereas at severe skin condition an increase in the level of nitrate anions, total NOS and its isoforms was observed with respect to the same in healthy individuals ($p<0.05$-0.01) (Table II).

Comparison of the indicators in patients with different severity of disease allowed detecting significant increase in nitrite anion content and decrease in nitrate anion level in patients with mild and moderate cases as compared to same in severe SJS ($p<0.05$).

Thus, the study of the indicators of NO-NOS system in patients with Stevens-Johnson syndrome showed the intensification of oxidative *L-Arginine* metabolism, expressed in different quantitative degree in SJS. The activity of total NOS was also maximal in patients with SJS - by 5.78 times. A significant increase in cNOS was observed in patients with SJS (by 1.81 times).

CONCLUSIONS

During the study, the intensity of nitric oxide system (NO-NOS) function was analysed and dependence of changes of its parameters from the clinical signs of Stevens-Johnson syndrome was detected. It was found that determination of nitrite and nitrate anion levels in blood serum can be used for the purpose of predicting the disease course and choosing the therapy methods for the patients with SJS.

Thus, it is feasible to combine complex therapy of patients with SJS with medications for the purpose of normalizing NOS isoforms activity and excessive production of nitric oxide (NO).

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Scietific research work

State registration number: 0116U004506
Cipher: IH. 25. 01. 0001. 16
Clinical and experimental justification of monitoring of diagnostics and standardized methods for treatment of metabolic disorders of internal organs and skin and their complications.

ORCID and contributionship:

Natalya V. Ivanyushko – Nazarko: 0000-0001-7524-9247 [A,B,C,D,E,F]
Orysya O. Syzon: 0000-0002-7011-2521 [A,D,E,F]
Svitlana V. Volbyn: 0000-0002-5066-3951 [A,E]
Tetyana I. Rudnyk: 0000-0002-4019-567X [A,B]
Marianna O. Dashko: 0000-0001-6441-5326 [D,E,F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Marianna O. Dashko
Danylo Halytsky Lviv National Medical University
1 Konovalets str., 79014 Lviv, Ukraine
tel: +380677691977; +380504131489
e-mail: mariannadashko@gmail.com

Received: 14.03.2020
Accepted: 03.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

ASSESSMENT OF ADULT EATING HABITS IN THE NUTRITIONAL PREVENTION OF STROKE

DOI: 10.36740/WLek202009203

Anna Sobalska[1], Katarzyna Tomczyk[1], Joanna Furman[1], Beata Łabuz-Roszak[1]
DEPARTMENT OF BASIC MEDICAL SCIENCES, FACULTY OF HEALTH SCIENCES IN BYTOM, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, BYTOM, POLAND

ABSTRACT

Introduction: Lifestyle modification, including changing eating habits, plays an essential role in the prevention of stroke.

The aim: The study aimed to assess the nutritional prevention of cerebrovascular diseases in adult inhabitants of Poland.

Material and Methods: The study was conducted using the author's questionnaire among 145 women and 76 men, aged 18 - 30 (53.9%) and 50 - 70 (46.1%) years.

Results: The following stroke risk factors were found in the examined group: overweight or obesity (46.6%), lack of regular physical activity (48%), smoking (33%), hypertension (22.1%), dyslipidemia (8.6%), diabetes (5.9%), and cardiac arrhythmias (6.3%).

The younger subjects compared to older ones more often declared the daily consumption of whole-grain cereal products and vegetables, fish at least once a week, and they preferred vegetable oils. On the other hand, older subjects declared the consumption of sweets, sweet drinks, salt, and fast food less frequently than younger ones. Also, fruits were more often chosen by older people. Both groups declared similar moderate consumption of milk and dairy products with reduced fat content, lean meat, and alcohol. Only 38% of respondents considered their eating habits to be appropriate.

Conclusions: The eating habits of examined adults only partially met the recommendations regarding the nutritional prevention of stroke. In some elements, younger people were more likely to follow appropriate dietary recommendations, while older people were more appropriate in others. The education regarding the principles of the nutritional prevention of cerebrovascular diseases is still necessary and should be age-appropriate.

KEYWORDS: cerebrovascular diseases, stroke, dietary prevention, eating habits, diet

Wiad Lek. 2020;73(9 p. II):1904-1911

INTRODUCTION

Cerebrovascular diseases constitute a significant public health problem in both developing and developed countries. Just after myocardial infarction and neoplastic diseases, they are among the main causes of death [1]. Mortality due to stroke in Poland is classified as one of the highest in Europe [2, 3].

The risk factors for cerebrovascular diseases, subject to modification, include arterial hypertension, ischemic heart disease, prior myocardial infarction, atherosclerotic stenoses of other arteries, heart disease (including arrhythmias), lipid metabolism disorders, hyperhomocysteinemia, diabetes, obesity, low physical activity, smoking and alcoholism [4-6]. The non-modifiable factors favoring the development of these diseases include age, sex, race, genetic factors, and a history of transient ischemic attack (TIA) or stroke [5, 7].

Changing lifestyle and diet play an essential role in the prevention of cerebrovascular diseases. A properly balanced diet can reduce the risk of developing a stroke, both in people who have not experienced symptoms of cerebral circulation failure (this is the so-called primary prevention) and in people who have had a stroke or TIA (it is the so-called secondary prevention). Prophylaxis aims to minimize the likelihood of the first or recurrent ischemic event, in particular, a stroke [8].

Fruits and vegetables are the basis of the stroke prevention diet. They are an essential source of vitamins, minerals, fiber, and antioxidants. It is recommended to eat them every day and with every meal. Each additional serving of vegetables and fruits reduces the risk of stroke by 5%. Dry legumes should also be included in the diet. They are a source of minerals, B vitamins, vitamin E, and a soluble fraction of dietary fiber [9].

It is recommended that the diet consists of whole-grain products with a low glycemic index, which are the main source of complex carbohydrates and dietary fiber [10]. The type and amount of fatty acids in the diet are essential in the prevention of cerebrovascular diseases. It is recommended to limit the consumption of total fat, saturated fatty acids, and trans fatty acid isomers in favor of food products rich in unsaturated fatty acids [11].

In the anti-stroke diet, it is recommended that you choose low-fat dairy products such as skimmed cheese and milk up to 1.5% fat. Fermented dairy products are also recommended, such as yogurt, kefir, and buttermilk, since they have a positive effect on blood cholesterol levels [9].

It is recommended to eat low-fat poultry and limit the consumption of red meat, rich in methionine [9]. It is

important to eat fish regularly, at least 2-3 times a week. Fatty sea fish are especially recommended due to the high content of omega-3 acids [12]. Table salt should be limited in the diet. Its consumption should not exceed 5 g/day, which corresponds to one teaspoon of salt [9].

It is crucial to choose the right heat preparation of food. Boiling, steaming, sleeve, or foil baking and stewing are recommended [9].

To reduce the risk of developing these diseases, it is crucial to maintain healthy body weight and to exercise regularly, at least 3-4 times a week. In addition to adequate nutrition and increased physical exertion, quitting smoking and limiting alcohol consumption also play a significant role [9].

The Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH) diet are particularly recommended in the prevention of cerebrovascular diseases. Both diets follow these dietary recommendations. The relationship between the Mediterranean diet and the improvement in the functioning of the vascular endothelium and the lipid metabolism profile has been demonstrated. There was also a decrease in blood homocysteine concentration, a reduction in blood pressure, and an increase in insulin sensitivity [13]. On the other hand, the DASH diet, in addition to reducing arterial hypertension, has an anti-atherosclerotic effect and prevents diabetes and obesity. Thanks to the use of this diet, the incidence of stroke can be reduced by up to 27% [10].

This study aimed to assess the eating habits of adults in the nutritional prevention of stroke.

MATERIALS AND METHODS

The research was carried out in December 2018. The research tool was an original questionnaire containing 24 questions. Nine of them concerned sociodemographic data and another fifteen - eating habits. The questionnaire was posted on websites and forums concerning healthy eating and the prevention of diet-related diseases. The participation of respondents in the study was voluntary and anonymous.

Two hundred twenty-one people took part in the study, including 145 women and 76 men. The respondents were divided into two age groups. The first group consisted of people between 18 and 30 years of age (n = 119; 53.9%), and the second group between 50 and 70 years of age (n = 102; 46.1%). Most of the study participants (n = 185; 83.7%) lived in the city, while the number of rural residents was 36 (16.3%). The largest percentage of respondents were people with higher education (n = 102; 46.1%). 87 respondents (39.4%) were people with secondary education, 27 people (12.2%) - with vocational, and 5 people (2.3%) - with primary.

Microsoft Excel from the Microsoft Office 2007 software and STATISTICA 10.0 (Stat Soft, Poland) were used to analyze the collected data.

RESULTS

The questions included in the questionnaire concerned the nutritional status of the respondents estimated using the body mass index (BMI) (Table I), a stroke history (Table II), and the presence of comorbidities that increase the risk of cerebrovascular diseases (Table III). Nutritional habits of adults in cerebrovascular disease prevention were assessed based on questions concerning their lifestyle (Table IV) and the frequency of consumption of particular food products (Table V).

Half of the respondents had an incorrect BMI value (n = 111; 50.2%) (Tab. I). The vast majority of respondents did not have a stroke (n = 212; 93.2%) (Tab. II). More than half of the respondents, i.e., 148 people (67%), did not suffer from any diseases mentioned in the questionnaire, which would increase the risk of cerebrovascular diseases. Among the studied group, the most common were arterial hypertension (n = 49; 22.1%), lipid metabolism disorders (n = 19; 8.6%), cardiac arrhythmias (n = 14; 6.3%) and diabetes (n = 13; 5.9%) (Tab. III).

Most of the respondents (n = 148; 67.0%) did not smoke. Thirty-nine people (17.7%) declared that they smoked cigarettes habitually. Sixty-one people (27.6%) admitted that they did not engage in physical activity. Forty-five people (20.4%) answered that they exercised several times a month, and 20 people (9.1%) - every day. More than 1/3 of the respondents (n = 84; 38.0%) believed that they had healthy eating habits. 70 (31.7%) of the respondents assessed their diet negatively, while the remaining 67 people (30.3%) could not assess it (Table IV).

The study group showed a low consumption of wholemeal grain products: 67 people (30.3%) consumed them every day, while 16 people (7.2%) did not eat them at all. Higher consumption of whole grain products was observed in the younger group.

Almost half of the respondents (n = 102; 46.1%) declared that they most often chose milk and dairy products with reduced fat content. Not much less, because 94 people (42.5%) answered that they most often chose full-fat milk and its products. The younger group more often chose full-fat dairy products than the older group.

Fatty types of meat were chosen more often by people in the older age group. 6.8% of the respondents (n = 15) did not eat meat at all. Almost half of the respondents (n = 100; 45.2%) consumed fish only a few times a month. Fish appeared on the menu once a week in 79 people (35.8%) - more often in the group of younger people. Seventeen subjects (7.7%) did not eat fish.

Slightly more than half of the respondents (n = 120; 54.3%) most often used vegetable oil - more often in the group of younger people. It was shown that more than half of the respondents (n = 129; 58.4%) consumed vegetables every day, while fruits were consumed every day by half of the studied group. Vegetables were eaten more often in the group of younger people, in contrast to fruits, which were more often chosen by people aged 50 - 70.

High consumption of sweets was observed in the studied groups: 160 people (72.4%) ate them at least once a week. Sweets appeared more frequently in the menus of younger

Table I. Nutritional status of the respondents (according to the BMI value).

Body mass index [kg/m^2]	N (%)
Underweight [< 18.5 kg/m^2]	8 (3.6)
Normal [18.5 - 24.9 kg/m^2]	110 (49.8)
Overweight [25.0 - 29.9 kg/m^2]	64 (29.0)
Obesity [> 30.0 kg/m^2]	39 (17.6)

Table II. Characteristics of answers to the question, "Have you had a stroke?"

Prior stroke	N (%)
Yes	9 (4.1)
No	212 (93.2)

Table III. The prevalence of selected diseases increasing the risk of cerebrovascular diseases

Disease	N (%)
Arterial hypertension	49 (22.1)
Diabetes	13 (5.9)
Dyslipidemia	19 (8.6)
Cardiac arrhythmia	14 (6.3)
Ischemic heart disease	5 (2.3)
Prior myocardial infarction	6 (2.7)
Other heart diseases	8 (3.6)
Stenosis or occlusion of carotid arteries	8 (3.6)
Atherosclerosis	9 (4.1)

Table IV. The lifestyle of the studied group.

	N (%)
Smoking	
Yes	39 (17.6)
No	148 (67.0)
Occasionally	34 (15.4)
Physical activity	
Everyday	20 (9.1)
5-6 times per week	13 (5.9)
3-4 times per week	34 (15.4)
1-2 times per week	48 (21.6)
Several times a month	45 (20.4)
Lack of any physical activity	61 (27.6)
Do you eat healthily?	
Yes	84 (38.0%)
No	70 (31.7%)
I do not know	67 (30.3%)

people. It was shown that sweet drinks were most often consumed occasionally (n = 82; 37.1%). Comparatively, but slightly more often, they were chosen by people from the younger group (n = 47; 39.5%). Alcohol was also consumed occasionally (n = 97; 43.9%), at a comparable level in both groups. Abstinence was declared more often by younger people (n = 17; 14.3%).

Slightly more than half of the respondents (n = 112; 50.7%) consumed fast food occasionally. This food was much less prevalent in the elderly group.

86% of respondents (n = 190) used salt in a moderate, low, or very little amount of salt. Salt was more often restricted in the elderly group (n = 93; 91.2%).

People in the 50 - 70 age group chose boiling/steaming (n = 80; 78.4%) as the most frequently used thermal treatment of dishes, while frying/grilling was chosen more often in the group of people aged 18 - 30 (n = 82; 68.9%) (Table V).

DISCUSSION

In addition to smoking and low physical activity, poor nutrition is one of the main risk factors for cerebrovascular diseases. The result of an inadequate diet and increased caloric intake is excess body weight. Overweight and obesity are serious problems of the 21st century because they affect an increasing number of people and predispose to the occurrence of other risk factors for the diseases in question.

In this study, abnormal body weight was shown in a significant proportion of the respondents. This problem was also noticed by Malczyk E. et al. in a study aimed at assessing the nutritional status of university employees in Opole, which showed that overweight and obesity concerned as many as 58% of the respondents [14].

When analyzing the fat content of the diet, it was observed that the majority of respondents chose meat with the low cholesterol content. Similar results were obtained by Król E. et al., where 90% of the respondents declared the consumption of lean meat. The significant consumption of red meat by almost half of the surveyed respondents was worrying [15].

Poland is one of the countries where fish consumption is low. The results obtained confirm this conclusion, as only 11.3% of people consumed the recommended amount of fish. This fact has also been confirmed by other authors. A study by Poręba R. et al. showed that only 22.6% of people ate fish two or more times a week [16]. Similar results were obtained by Król E. et al., where 20% of people reported eating fish several times a week [15].

In this study, optimistic results were obtained for the type of fat used in the daily diet. Vegetable oil was most often chosen by the respondents. The research conducted by Poręba R. et al. showed that butter was the most frequently preferred type of fat among students from Wrocław universities [16]. A positive aspect in the area of the eating habits of the studied group was the reduction of salt in the daily diet. The same tendency was noticed in the study by Poręba R. et al., which examined the lifestyle and risk factors of cardiovascular diseases among students of the University of Wrocław [16].

The fact that alcohol consumption is common in the study group, which was also stated by other authors, raises concerns. Poręba R. et al. in the conducted study noted that nearly 90% of respondents consumed alcohol. Almost 30% of the respondents used it at least once a week. The vast majority of people consumed alcohol occasionally [16].

Table V. Comparison of eating habits in the group of younger and older people (N = 221).

	All (N = 221) n (%)	18 - 30 years (N = 119) n (%)	50 - 70 years (N = 102) n (%)
The frequency of consumption of whole grain products			
Every day	67 (30.3)	39 (32.8)	28 (27.5)
Less often	138 (62.5)	72 (60.5)	66 (64.7)
I do not eat	16 (7.2)	8 (6.7)	8 (7.8)
Fat content in the consumed milk and dairy products			
Full fat	94 (42.5)	56 (47.0)	38 (37.2)
Skimmed	102 (46.2)	54 (45.4)	48 (47.1)
Without fat	10 (4.5)	5 (4.2)	5 (4.9)
I do not eat	15 (6.8)	4 (3.4)	11 (10.8)
The type of meat consumed			
Lean	188 (85.1)	99 (83.2)	89 (87.3)
Fat	164 (74.2)	73 (61.3)	91 (89.2)
I do not eat	15 (6.8)	7 (5.9)	8 (7.8)
The frequency of fish consumption			
Several times a week	25 (11.3)	11 (9.2)	14 (13.7)
Once a week	79 (35.8)	36 (30.3)	13 (12.7)
Several times a month	100 (45.2)	58 (48.7)	42 (41.2)
I do not eat	17 (7.7)	14 (11.8)	33 (32.4)
The type of fat most commonly used			
Vegetable oil	120 (54.3)	74 (62.2)	46 (45.1)
Butter / margarine / lard	99 (44.8)	44 (37.0)	55 (53.9)
I do not use	2 (0.9)	1 (0.8)	1 (1.0)
The frequency of consumption of vegetables			
Every day	129 (58.4)	77 (64.7)	52 (51.0)
Less often	89 (40.3)	41 (34.5)	48 (47.1)
I do not eat	3 (1.4)	1 (0.8)	2 (1.9)
The frequency of fruit consumption			
Every day	112 (50.7)	50 (42.0)	62 (60.8)
Less often	109 (49.3)	69 (58.0)	40 (39.2)
I do not eat	0 (0.0)	0 (0.0)	0 (0.0)
The frequency of consumption of sweets			
At least once a week	160 (72.4)	93 (78.2)	67 (65.7)
Several times a month	22 (10.0)	10 (8.4)	12 (11.8)
Occasionally	38 (17.2)	15 (12.6)	23 (22.5)
I do not eat	1 (0.5)	1 (0.8)	0 (0.0)
The frequency of consumption of sweet drinks			
At least once a week	65 (29.4)	37 (31.1)	28 (27.5)
Several times a month	22 (10.0)	10 (8.4)	12 (11.8)
Occasionally	82 (37.1)	47 (39.5)	35 (34.3)
I do not eat	52 (23.5)	25 (21.0)	27 (26.4)
The frequency of alcohol consumption			
At least once a week	63 (28.5)	31 (26.1)	32 (31.4)
Several times a month	35 (15.8)	18 (15.1)	17 (16.7)
Occasionally	97 (43.9)	53 (44.5)	44 (43.1)
I do not eat	26 (11.8)	17 (14.3)	9 (8.8)
The frequency of consumption of fast food			
At least once a week	18 (8.1)	14 (11.8)	4 (3.9)
Several times a month	40 (18.1)	32 (26.9)	8 (7.9)
Occasionally	112 (50.7)	62 (52.1)	50 (49.0)
I do not eat	51 (23.1)	11 (9.2)	40 (39.2)
The amount of salt consumed			
Very big/big	26 (11.8)	18 (15.1)	8 (7.8)
moderate / small / very small	190 (86.0)	97 (81.5)	93 (91.2)
I do not use	5 (2.3)	4 (3.4)	1 (1.0)
Type of heat treatment applied			
Boiling / steaming	164 (74.2)	84 (70.6)	80 (78.4)
Baking	96 (43.4)	50 (42.0)	46 (45.1)
Stewing	47 (21.3)	24 (20.2)	22 (21.6)
Frying / grilling	137 (62.0)	82 (68.9)	55 (53.9)

An essential element in the principles of healthy eating is the selection of appropriate thermal processing of food. The obtained results indicate that the most frequently used culinary techniques were frying/grilling (62.0%) and boiling in water/steaming (74.2%). In the study by Pudło H. and Respondek M., 57% of respondents also used frying [17]. The results obtained by Król E. et al. indicated that as many as 69% of respondents used frying, which is one of the inadvisable methods of cooking food. Only 31% of people cooked in water and steam [15].

This study shows a low level of physical activity in the majority of respondents. The lack of physical activity concerned even 1/3 of the respondents. Similar results were obtained in the WOBASZ study (Multicenter National Population Health Survey) [18].

In recent years, there have been fewer nicotine addicts. However, the situation remains unsatisfactory. Smoking is a significant risk factor of cardiovascular diseases. Among the respondents, the percentage of smokers was 33%, which was a similar result compared to the results obtained in the WOBASZ study, in which smokers accounted for 33.5% [18]. The research conducted so far on lifestyle, and the assessment of eating habits shows that Polish society is particularly exposed to risk factors for cerebrovascular diseases.

CONCLUSIONS

The eating habits of the study group only partially met the recommendations for the prevention of cerebrovascular diseases. In some respects, the proper dietary recommendations were more often followed by younger people, and in others by older people. Pro-health education on the principles of proper nutrition in the field of stroke prevention is still necessary and should be conducted in a manner appropriate to the age group.

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ORCID and contributionship

Anna Sobalska - 0000-0003-2800-2238 [A-D]
Katarzyna Tomczyk - 0000-0002-1978-4920 [C-D]
Joanna Furman - 0000-0002-6013-5105 [C-D]
Beata Łabuz-Roszak - 0000-0002-9835-8240 [A,C,E-F]

Conflict of interest

Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Beata Łabuz-Roszak
Department of Basic Medical Sciences
Faculty of Health Sciences in Bytom,
Medical University of Silesia in Katowice,
ul. Piekarska 18, 41-902, Bytom, Poland;
tel: +48 605097110
email: beatamaria.pl@hoga.pl

Received: 14.07.2020
Accepted: 12.09.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

CLINICAL AND LABORATORY PREDICTORS OF DIGESTIVE SYSTEM DISEASES IN HIV-INFECTED PATIENTS FOR FAMILY MEDICINE PRACTICE

DOI: 10.36740/WLek202009204

Olga A. Golubovska, Volodymyr I. Vysotskyi
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

The aim: To identify clinical and laboratory signs of digestive system disease in HIV-infected patients for helping family physicians.

Materials and methods: Research was conducted at five regional HIV / AIDS centers in Ukraine during 2017-2019. Randomly selected 342 adult HIV-infected patients were divided into two groups, with concomitant digestive system diseases and without concomitant digestive system disease. Statistical analysis was performed using the software package EZR 1.41 (Saitama Medical Center, Jichi Medical University, Japan).

Results: The incidence of digestive system disease in patients with HIV clinical stages II, III and IV was significantly higher than in patients with HIV clinical stage I. Gastrointestinal disease was also significantly associated with the incidence of tuberculosis, candidiasis, kidney disease and HIV encephalopathy. Incidence of asthenic-vegetative and dyspeptic syndromes, weight loss, anemia and leukopenia, elevated liver enzymes, low CD4 counts and detectable viral load levels in patients on antiretroviral therapy were significantly more common in HIV-infected patients with gastrointestinal pathologies. HIV patients with digestive system disease significantly more often had changes to their therapy regiment, interruptions in treatment and more often experienced side effects.

Conclusions: Digestive system disease becomes more common with the progression of HIV infection. Comorbidity of HIV infection and digestive system disease is characterized by changes in general clinical, biochemical and immunological blood parameters and patients with digestive system comorbidities more often have a poor virological response to antiretroviral therapy.

KEY WORDS: HIV infections, digestive system diseases, family medicine

Wiad Lek. 2020;73(9 p. II):1909-1914

INTRODUCTION

Ukraine has one of the largest HIV epidemics in Eastern Europe and Central Asia by the number of new HIV / AIDS cases. According to the rate of HIV / AIDS spread in Europe and the world, Ukraine is second and fifth, respectively, and ranks 22nd among 123 countries in terms of the estimated number of people living with HIV [1,2].

The key priority of health and social policy in Ukraine is to fight diseases that have the greatest negative socio-demographic and economic impact and together with their associated pathologies form the main burden of infectious diseases in Ukraine and lead to reduced life expectancy, comorbidities and concomitant diseases, disability and premature mortality. With this in mind, the problem of improving the effectiveness of monitoring and treatment of both opportunistic infections and other somatic conditions in HIV-infected patients is a strategic and operational objective of the State Strategy for fighting HIV / AIDS, tuberculosis and viral hepatitis by 2030 and ensuring comprehensive access to HIV treatment [3].

At the same time, the UNAIDS Strategy 2016-2021 On the Fast-Track to end AIDS emphasizes the importance of strengthening and expanding the provision and adherence to antiretroviral therapy (ART) including increasing services aimed at treating co-infections and concomitant pathologies and providing prevention, treatment, care and support services for HIV-infected patients. This requires improving and expanding the integration of care for HIV-infected patients with the treatment of other chronic comorbid conditions, so that the patient-centered clinical monitoring of lifelong ART can provide the best outcome for the patient and help achieve the global goal of ending the HIV epidemic [4].

Digestive system (DS) diseases in Ukraine are the 3rd in prevalence among the whole population (9.8%) and hold the 7th place in causes of morbidity (4.1%). Given that DS diseases affect all age groups, and most patients are of working age, the medical and social relevance of DS diseases is high [5,6]. Given the frequency of comorbidity of HIV infection with diseases of the DS, it is important to study the possibilities of their early diagnosis to prevent the risk of complications, interruptions to continuous antiretroviral therapy (ART) and nonadherence to ART due to DS pathology complications.

International experience of more active involvement of at-risk patients and primary care clinicians in the treatment, spot testing and use of streamlined hepatitis B and C management algorithms has demonstrated improved patient and

community care [7]. It is emphasized that family physicians play a key role in the detection and treatment of many chronic gastrointestinal complications in HIV-infected patients and the monitoring of frequently used drugs [8]. To improve lifelong access to continuous ART, the importance of decentralizing the provision of HIV services to the level of primary care facilities is obvious, including authorize prescription of ART at primary care centers [9]. General practitioners of family medicine are responsible for providing continuous, coordinated and comprehensive integrated health care for all categories of patients and managing the numerous needs of patients, regardless of the nosology of the disease, which is in line with international strategies to combat the HIV epidemic [10-12].

This is especially important in the context of health care system reforms in Ukraine, where family physicians must provide medical care to all patients including those with HIV infection and concomitant pathologies as part of primary care [13,14]. Thereby, the problem of studying the current situation along with the ways to improve and form a modern, comprehensive, patient-oriented approach to help family physicians treat HIV-infected patients with comorbid somatic pathologies of the digestive system becomes especially poignant.

THE AIM

The aim of the study was to identify clinical and laboratory signs of digestive system comorbidities in HIV-infected patients with the end goal of helping family physicians more easily diagnose such patients and provide them with patient-oriented care and support.

MATERIALS AND METHODS

The research was conducted on the clinical bases of the Department of Infectious Diseases and the Educational and Research Center - Ukrainian Family Medicine Training Center of the Bogomolets National Medical University (Kyiv, Ukraine), included the Kyiv City Center for AIDS Prevention and Control at the Kyiv Clinical Hospital №5 and four regional HIV / AIDS centers in Odesa, Kherson, Mykolaiv and Dnipropetrovsk regions during 2017-2019.

Data from medical cards of outpatients, including medical history extracts of inpatient treatment and HIV patient dispensary supervision cards were used. To preserve the anonymity of patients, all medical documents were coded and numbered. Data collection was conducted in compliance with the requirements of existing bioethical norms and scientific standards.

To achieve the objectives of the study, 342 patients who were registered at the HIV / AIDS Centers and had a confirmed diagnosis of HIV infection were selected by randomized sampling from 12680 total patients.

The inclusion criteria were as follows: the patient had a verified diagnosis of HIV infection, male or female, aged 18 years or older. Exclusion criteria: child and adolescent HIV-infected patients.

Medical records were examined for general clinical methods of examination (anamnestic, assessment of general condition, physical examination) used to diagnose gastrointestinal pathology and to establish the clinical picture. Hematological and biochemical studies were used to identify the state of hematopoiesis, indicators of hepatocyte cytolysis, bilirubin metabolism, synthetic liver function and excretory function of the kidneys. Serological tests in dynamics were used to detect antibodies to HIV, hepatitis C virus and hepatitis B virus. Molecular genetic methods were used to confirm diagnoses of HIV infection, chronic viral hepatitis and to monitor the course of the disease and the effectiveness of therapy. Instrumental tests (fibrogastroduodenoscopy, chest radiography, computed tomography of the chest and abdomen, sonography of the abdominal cavity) were used to determine the condition and detect pathological changes in the relevant organs and systems. The diagnosis of HIV infection was established and confirmed on the basis of existing recommendations and protocols.

The assignment of patients into groups was carried out based on the presence or absence of digestive system (DS) disease. The main group (MG) consisted of 252 patients with pathology of the DS. The control group (CG) consisted of 90 patients without signs of damage to the DS. The groups are comparable in age and sex composition. Patients with II, III and IV HIV clinical stage predominated in the MG, in the CG more than half the patients were in stage I (Table 1).

Statistical processing of the data was performed using the EZR 1.41 software package (Saitama Medical Center, Jichi Medical University, Japan).

RESULTS AND DISCUSSION

The nature of concomitant gastrointestinal disease observed in patients in the main group and the control group was analyzed. Tuberculosis ($p < 0.01$), candidiasis ($p < 0.05$), kidney disease ($p < 0.001$) and HIV encephalopathy ($p < 0.01$) were significantly more often observed in the main group. Using the Chi-squared test ($\chi 2$) the relationship between having digestive system disease and other comorbidities as a factor that increases its likelihood was determined. The relationship is considered significant in cases where the confidence interval does not contain the null value of 1. (Table II).

It was found that patients with candidiasis and tuberculosis were twice as likely to have DS disease and in the presence of HIV encephalopathy and kidney disease the chance of having DS disease was 4.5 and 3.7 times more likely, respectively.

The majority of patients in the main group with DS disease, 150 (59.5%) patients, ($p < 0.001$), had two or more organs affected by digestive system pathologies. Hepatitis of various etiologies - viral, toxic or of unknown etiology was the most common DS disease. A total of 220 (87.3%) main group patients were diagnosed with hepatitis ($p < 0.001$). Hepatitis diagnoses included chronic hepatitis C

Table I. Baseline characteristics of patients included in the study

	Main group	Control group
Number of patients	252	90
Male	140 (55,6%)	47 (52,2%)
Female	122 (44,4%)	43 (47,8%)
Average age	42,7±0,6	38,7±1,1
Median age	42	38
HIV clinical stage I	43 (17,1%)	51(56,7%)
HIV clinical stage II	25 (9,9%)	5 (5,6%)
HIV clinical stage III	69 (27,4%)	7 (7,8%)
HIV clinical stage IV	115 (45,6%)	27 (30,0%)

Table II. The odds ratio of patients having DS disease in the presence of other comorbidities

Variables	Odds Ratio	Standard Error	95% Confidence Interval
Candidiasis	2,055	0,262	1,229-3,436
Tuberculosis	1,961	0,302	1,086 - 3,541
HIV encephalopathy	4,471	0,447	1,860-10,747
Kidney disease	3,696	0,489	1,418-9,631

(HCV) - 118 (46.8%), HCV and hepatitis of unknown etiology together - 10 (4.0%), chronic hepatitis B (HBV) - 9 (3.6%) HCV and HBV - 9 (3.6%) and hepatitis of unknown etiology - 74 (29.4%) of the patients. The second most common DS disease was chronic pancreatitis in 116 (46.0%) patients. It is noteworthy that only 4 (3.4%) patients had pancreatitis as a DS monopathology, in the remaining 112 (96.6%) pancreatic disease was combined with other DS diseases. Gastro-duodenal disease was found in 88 (34.9%) patients. Gastroduodenitis was diagnosed in 47 (53.4%), gastritis in 14 (15.9%), and peptic ulcer disease in 4 (4.5%) patients. The remaining 23 (26.1%) patients had multiple gastric pathologies.

Chronic cholecystitis was found in 74 (29.4%) patients, of which 66 (89.2%) was acalculous and 8 (10.8%) was calculous. Of these, 56 (75.7%) patients had cholecystitis combined with pancreatitis 38 (51.4%) and other DS diseases, 8 (10.8%) with chronic hepatitis, 5 (6.8%) with gastroduodenal lesions, 3 (4.1%) with chronic hepatitis, gastroduodenitis or gastritis, and 2 (2.8%) with colitis and chronic hepatitis or gastritis. Only one patient (1.7%) had calculous cholecystitis as a monopathology.

Candidal esophagitis was observed in 13 (5.2%) of the patients. As it is a manifestation of severe immunodeficiency it was observed only in stage IV HIV-infected patients and was combined with chronic hepatitis and gastroduodenitis or gastritis in 6 (46.2%) patients, with chronic hepatitis in 4 (30.8%) patients, with chronic hepatitis, pancreatitis and peptic ulcers in 3 (23.1%) patients. Colitis was observed in 8 (3.2%) patients and only in one case (12.5%) was the only diagnosed gastrointestinal disease.

Distribution of patients with DS diseases by the clinical stage of HIV infection (Fig. 1).

Digestive system pathologies were more frequent as HIV infection progressed. In patients with clinical stages II, III and IV they were observed significantly more often than in patients with clinical stage I. Of patients in HIV clinical stage I 43 (45.7%) had gastrointestinal disease ($p > 0.05$), 30 (83.3%) in clinical stage II ($p < 0.05$), 69 (90.8%) in stage III ($p < 0.05$) and 115 (81.0%) with IV clinical stage ($p < 0,05$).

The frequency DS disease in patients with different clinical stages of HIV infection was compared. It was found that for HCV and HBV infections and for hepatitis of unknown etiology the association with the stage of HIV infection was not significant ($p > 0.05$). There was also no statistical difference in the frequency of detection of cholecystitis ($p > 0.05$). On the contrary, there was a statistically significant relationship between HIV clinical stages and the frequency of gastroduodenitis and pancreatitis ($p < 0.01$ and $p < 0.05$, respectively).

The following symptoms were observed statistically more often in the MG patients then in the CG patients (Table III).

Other symptoms, such as headache, pallor, vomiting, heartburn, diarrhea, bloating, cough, and rashes were observed in MG and CG patients with the same frequency ($p > 0.05$).

Antiretroviral therapy was prescribed in accordance with existing protocols and recommendations. Therapy changes and interruptions in treatment, as well as the frequency of adverse reactions in the main group were significantly more frequent than in the control group, $p < 0.05$. The most common side effects that required therapy correction were lack of immune response, hematotoxic effects manifested by the development of anemia, leukopenia, thrombocytopenia or pancytopenia, lipodystrophy, and severe dyspeptic syndrome in the form of nausea, vomiting

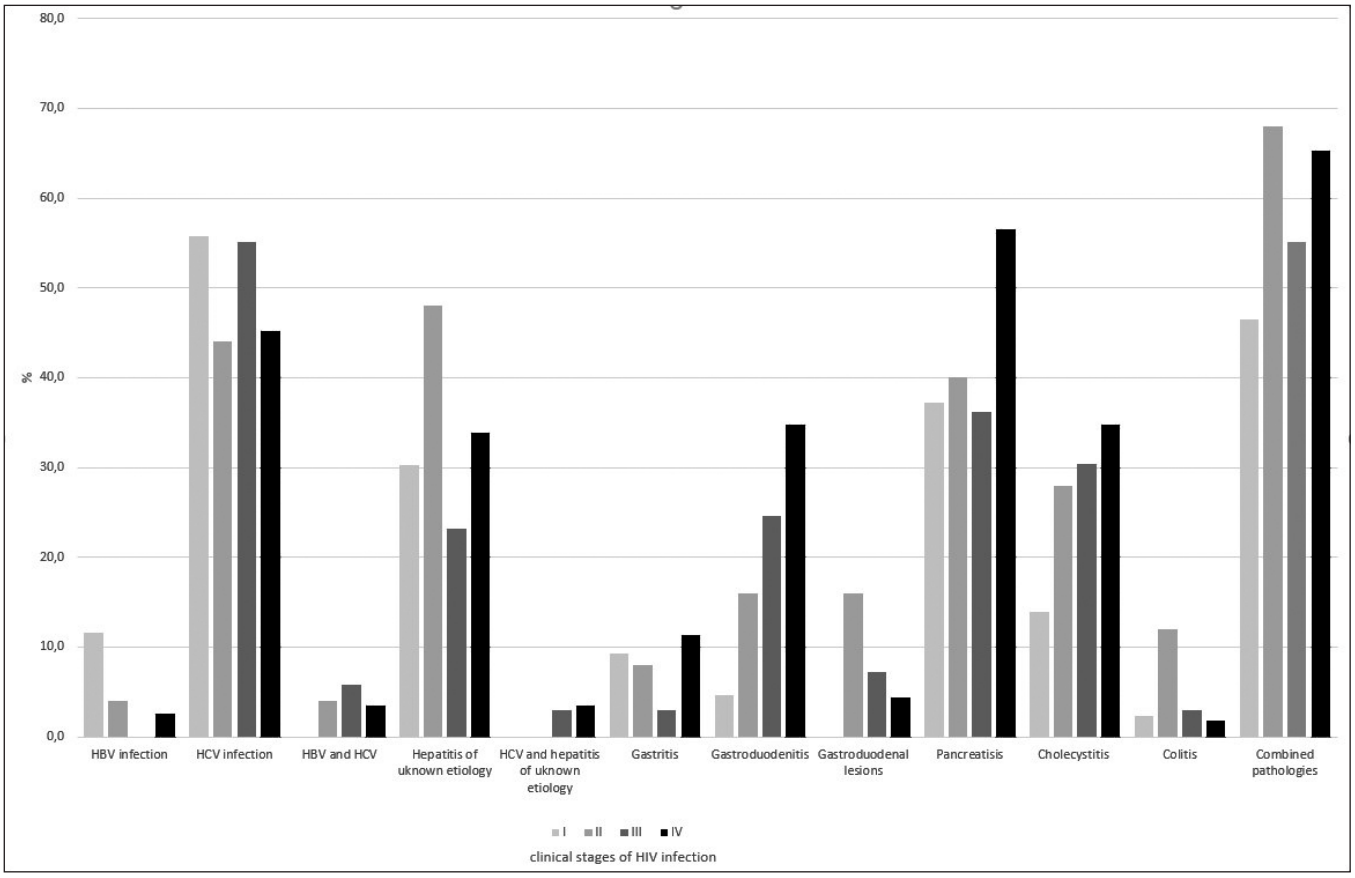

Fig 1. Distribution of DS diseases in patients with different clinical stages of HIV infection.

Table III. Clinical symptoms in HIV-infected patients in the MG and the CG

Symptoms	Main Group		Control Group		P
	N	%	N	%	
Weakness	123	48,8	17	18,9	<0,001
Weight loss	66	26,2	9	10,0	<0,01
High temperature	63	25,0	8	8,9	<0,01
Cognitive disorders and neurological issues	54	29,0	6	8,9	<0,01
Loss of appetite	67	26,6	7	7,8	<0,001
Nausea	45	17,9	2	2,2	<0,001
Epigastric pain	49	19,4	7	7,8	<0,05
Itchy skin	24	9,5	1	1,1	<0,01

and pain. Significantly more patients in the main group experienced adverse effects of ART: hematotoxicity was experienced by 18 (81.8%) MG patients and 4 (18.2%) CG patients ($p < 0.05$), lack of immunological response by 20 (87%) MG patients and 3 (13%) CG patients ($p < 0.05$), lipodystrophy by 6 (85.7%) MG patients and only 1 (14.3%) CG patient ($p < 0.05$), dyspeptic syndrome by 9 (100%) and 0 CG patients ($p < 0.05$).

The frequency and nature of hematological changes in MG and CG patients were analyzed. Anemia with a decrease in hemoglobin below 120 g/L in women and 130 g/L in men was observed in 94 (48.5%) MG patients and 11 (34.5%) CG patients ($p < 0.05$).

Leukopenia with a leukocyte count below $4.0x10^9$ /L was detected in 59 of 193 MG patients (30.6%) and in 4 of 28 CG patients (14.3%) ($p < 0.05$). Leukocytosis, on the contrary, was significantly more common in CG, 6 of 28 patients (21.4%) compared with 8 of 193 (4.2%) MG patients ($p < 0.05$). An increase in erythrocyte sedimentation rate of more than 10 mm/hour in men and 15 mm/hour in women was found in 95 of 193 (58.6%) MG patients and in 9 of 18 (50.0%) CG patients, the difference was not statistically significant ($p > 0.05$).

There was no statistically significant difference between the mean hemoglobin, erythrocyte count and erythrocyte sedimentation rate ($p > 0.05$) between groups. The average

level of leukocytes in the control group was statistically significantly higher than in the main group ($p < 0.05$).

The biochemical parameters present in all blood profiles were analyzed. Overall biochemical blood profiles were available for 117 of 252 MG patients (46.4%) and 42 of 90 CG patients (46.7%) ($p > 0.05$). Low total protein levels and hypoalbuminemia in patients in both groups were observed with almost equal frequency ($p > 0.05$). Increased alanine aminotransferase (ALT) levels were found in MG patients significantly more often due to the inclusion in this group of patients with viral and toxic liver disease of various etiology ($p < 0.05$). Elevated gamma-glutamyl transferase (GGT) levels were also significantly more common in the main group ($p < 0.05$), which included patients with hepatitis and pancreatitis and significantly more patients with kidney disease than in the control group (17.9% and 5.6% respectively, $p < 0.01$). Probably for the same reason, MG patients were statistically significantly more likely to have elevated levels of urea and creatinine ($p < 0.05$).

When comparing the average values of various biochemical blood tests, no statistically significant differences were found between groups in the average values of total protein, albumin, urea and creatinine levels ($p > 0.05$). However, the average levels of ALT and GGT were statistically higher in the main group ($p < 0.05$).

The results of immunological tests showed that a moderate decrease in the CD4 lymphocyte count was observed in 96 of 234 (41.0%) examined main group patients and in 25 of 71 (35.2%) control group patients. The difference was not statistically significant ($p > 0.05$). However, CD4 lymphocyte counts which correspond to a state of severe immunodeficiency were found in the main group in 63 (26.9%) patients against 9 (12.7%) in the control group, and normal values were 75 (32.1%) patients in the main group and 37 (52.1%) in the control group. That is, MG patients were more likely to have advanced immunodeficiency and lower CD4 counts, with a statistically significant difference, $p <0.05$ and $p <0.01$, respectively. The average CD4 count in the main group was 418.96 ± 18.26 cells/μl (Me = 394, Mo = 190) and was statistically significantly lower than in the control group, 548.7 ± 40.15 cells/μl (Me = 525.5, Mo = 808), ($p <0.01$).

The results of virological testing showed that the vast majority of HIV-infected patients in the study 174 (69.0%) in the main group and 79 (87.8%) in the control group achieved a good virological response to ART with a viral load of less than 40 copies/ml ($p < 0.05$). However, there were 78 (31.0%) patients in the main group whose viral load was above detectable levels, which was statistically significantly higher than in the control group, which had 11 (12.2%) patients ($p < 0.05$).

The presence of untreated comorbid diseases of the digestive system in HIV-infected patients may be a predictor of reduced effectiveness of ART. Therefore, the role of primary care physicians, and especially family physicians, in ensuring the timely detection, monitoring and treatment of typical digestive diseases in HIV-infected patients is crucial.

This is especially relevant in primary care facilities, where family physicians are entrusted with the provision of medical care to patients with HIV and treating their concomitant somatic pathologies. Primary care institutions carry out seroepidemiological monitoring of HIV infection spread, including tracing HIV transmission routes, as well as reporting deaths among HIV-infected patients, according to the order № 180 from 05.03.2013 of the Ministry of Health of Ukraine [15].

That is, these above-mentioned activities of the current primary care practice and policies aim to create a modern integrated, patient-oriented approach to the management of these nosologies in family medicine practice, which would be in line with international strategies to counteract the HIV epidemic, which emphasize the importance of expanding and implementing patient-oriented care strategies.

CONCLUSIONS

1. Digestive system disease was found in 73.7% of examined HIV-infected patients. The most common DS diseases found were chronic viral hepatitis, chronic hepatitis of unknown etiology, gastroduodenal disease, chronic and cholecystitis. The majority of patients had multiple organs affected by DS diseases. The incidence of DS diseases increased with the progression of HIV infection and was diagnosed in HIV-patients with clinical stages II, III and IV significantly more often than in patients with stage I.
2. HIV-infected patients with DS diseases were found more likely to complain of asthenic-vegetative syndrome symptoms.
3. ART regimen changes, interruptions in treatment and side effects of ART were found to occur significantly more frequently in patients with DS diseases.
4. Anemia, leukopenia, increased ALT and GGT levels, CD4 and lymphocyte counts below 500 cells/ml and a detectable viral load level while on ART ($p < 0.05$) were significantly more common in HIV patients with DS diseases.
5. Markers of gastrointestinal comorbidities in HIV-infected patients are available for monitoring and control in medical records of primary care practices in Ukraine and can be used for timely detection, monitoring and treatment of typical digestive system diseases by family physicians.

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The work is performed within the framework of the research work of Educational and Research Center - Ukrainian Family Medicine Training Center and Department of Infection Diseases of Bogomolets National Medical University "Development of a system to counteract the spread of socially dangerous hemocontact viral infections at the level of primary health care in the context of public health of Ukraine" under the support of the Ministry of Health of Ukraine. State registration number: 0118U001212.

ORCID and contributionship:
Olga A. Golubovska: 0000-0003-3455-8718 [A, E, F]
Volodymyr I. Vysotskyi: 0000-0001-6010-6614 [A, B,C, D, E, F]

Conflicts of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Volodymyr I. Vysotskyi
Bogomolets National Medical University
19/11, Schussev str., apt.9, 04060 Kyiv, Ukraine
tel: +380674077781
e-mail: vysotskyiv@gmail.com

Received: 10.04.2020
Accepted: 29.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

OPTIMUM DURATION OF PERCUTANEOUS TRANSHEPATIC CHOLANGIODRAINAGE IN COMMON BILE DUCT DISEASES COMPLICATED BY OBSTRUCTIVE JAUNDICE

DOI: 10.36740/WLek202009205

Anastasiia L. Sochnieva
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: is to determine the optimum duration of percutaneous transhepatic cholangiodrainage depending on the duration of obstructive jaundice and the baseline total bilirubin level in patients with benign and malignant common bile duct diseases complicated by obstructive jaundice.

Materials and methods: The experience of applying percutaneous transhepatic cholangiodrainage was combined for 88 patients with common bile duct diseases complicated by obstructive jaundice. The patients were divided into three groups: the Group 1 included 15 patients (17.1%) with benign common bile duct diseases, the Group 2 included 11 patients (12.5%) with resectable cholangiocarcinomas, and the Group 3 included 62 patients (70.4%) with unresectable cholangiocarcinomas. To determine optimal terms of biliary decompression using percutaneous transhepatic cholangiodrainage, the Poisson process was applied, and, to be more precise, the quasi-Poisson distribution.

Results: It was found that the reduction of total bilirubin was the fastest in Group 3 patients. It took these patients an average of 7-8 days to reduce total bilirubin to 50 μmole/l. In Group 1 patients, the process is somewhat slower. The duration of biliary decompression in this category of patients averages 10-12 days. For Group 2 patients, biliary decompression requires at least 12 days.

Conclusions: Using the Poisson process, or, to be more precise, the quasi-Poisson distribution, we managed to determine the optimum duration of biliary decompression using percutaneous transhepatic cholangiodrainage depending on the obstructive jaundice duration and the baseline total serum bilirubin.

KEY WORDS: main bile duct disease, obstructive jaundice, antegrade endobiliary interventions, serum bilirubin level

Wiad Lek. 2020;73(9 p. II):1915-1925

INTRODUCTION

Hyperbilirubinemia is an integral symptom of biliary hypertension. The latter appears as a result of an increase in serum bilirubin concentration, which in turn is due to the penetration of urine components into blood. When the serum bilirubin level is above 40 μmole/l, the clinical signs of obstructive jaundice (OJ) are seen with the naked eye [1].

Pathological changes of liver and other organs and systems are a consequence of disrupted bile outflow. The main cause of hepatocyte necrosis is the progression of dystrophic changes, which leads to the risk of the development of secondary biliary liver cirrhosis. Changes in the histological liver structure, disruption of the intrahepatic blood flow, and, as a consequence, the development of portal hypertension and ascites are observed at late stages of OJ [2].

Hepatic insufficiency as a manifestation of secondary biliary liver cirrhosis at the background of OJ still remains the most frequent and dangerous complication of bile duct diseases and, in at least 50% of cases, it becomes the cause of lethal outcomes in patients during the post-operative period [3].

Cholestasis contributes to favorable conditions for the development of cholangitis. The most rapid development of irreversible changes in the liver is observed when total obstruction of the common bile duct is combined with the presence of pyoinflammatory processes in bile ducts [4, 5].

The cause of bile duct obstruction can be both benign and malignant common bile duct diseases [6, 7].

Persistent OJ is accompanied by headache and skin itching. The above symptoms are due to the toxic influence on the nervous system. The endothelium of brain vessels are affected in case of increased concentration of bilirubin and bile acids in blood. It does not only disrupt cerebral blood circulation and enhances their influence on it, but also entails functional changes in the central nervous system. The liver itself is not able to neutralize the products of nitrogen decomposition (increased ammonia level) formed in large amounts, which intensifies its toxic influence. By reflex, bile acids enhance the tone of the vagus nerve, which is manifested by bradycardia and becomes a sign of blood circulation disorder in case of obstructive jaundice. Moreover, the sinoatrial node is affected by the toxic influence of bile acids. Hypocoagulation disorders of the blood coagulation system take place at the background of inadequate vitamin K absorption and lead to hemorrhages and hematoma formation. As a result of damaged tubules and glomeruli, water and sodium absorption gets disrupted. The hepatorenal syndrome develops, which is characterized by increased arterial pressure, proteinuria

and swelling. Disrupted passage of bile to the digestive tract implies the threat of pronounced dysbiotic changes, such as reduced count of anaerobes and increased count of aerobes and opportunistic pathogenic microflora [2].

The main cause of lethal outcomes in OJ is hepatic impairment. Regardless of OJ etiology, the course of hepatic impairment is uniform in all patients. Hepatic impairment is aggravated by the following factors: tumor intoxication, cholangitis, bleeding, general anesthesia, operational trauma. The frequency and severity of post-operative complications directly depend on the grade and duration of hyperbilirubinemia. Serum bilirubin above 200 μmole/l is considered hazardous, and above 400 μmole/l critical for the development of hepatic impairment. An increase in the level of urea and serum creatinine is an adverse prognostic factor [7].

The development of morphological and functional changes in the liver are due to persistent cholestasis and biliary hypertension. The latter lead to the development of hepatic impairment, purulent cholangitis and thrombo-hemorrhagic syndrome. The majority of these patients are aged 60 or older. At this age, the main disease in many patients is accompanied by severe comorbidities that dictate the need for choosing the least traumatic surgical treatment tactics [8, 9].

Disturbance of the enteropathic circulation of bile acids, penetration of cholestasis components and their toxic influence on hepatocytes lead to the development of destructive changes in the liver in OJ. The inhibition of cellular respiration, damage of lipid cellular membranes and subcellular structures, disruption of oxidizing phosphorylation processes and destruction of hepatic cells are due to the presence of excessive bound and unbound urine components in blood [2].

Dysproteinemia, disturbance of lipid and carbohydrate metabolism, shift of the electrolyte and acid-base balance, accumulation of toxic metabolism products are responsible for the development of endogenous intoxication and are biochemical signs of hepatocyte damage [10].

Treatment results directly depend on the OJ severity grade. Despite the rapid development of hepatobiliary surgery, there is no unified classification [11, 12, 13].

Many researchers relate OJ severity to the baseline serum bilirubin level. Thus, V. Fedorov et al. classify hyperbilirubinemia below 100 μmole/l as mild OJ, 100-200 μmole/l as moderate OJ and above 200 μmole/l as severe OJ [14].

Other authors use several factors for determining the severity of OJ. Dixon J. M. et al. singled out three independent factors correlating with post-operative complications and mortality: hematocrit below 30%, bilirubin above 200 μmole/l and malignant OJ etiology [15].

The proposed classifications and grading scales are rather labor-intensive, detailed and based on complex etiopathogenetic and morphofunctional data that are difficult to apply in clinical practice. The process of assessing OJ severity should be based on clinical signs and generally acceptable laboratory data that can be easily used in the surgeon's everyday practice.

The simplicity of the severity assessment concept is presented in the Child-Pugh classification that is widely used for patients with hepatic cirrhosis. It has become a globally recognized and commonly used severity scale. Unfortunately, this scale cannot be applied for assessing OJ severity [16, 17].

The majority of authors believe that, at bilirubin levels below 50 μmole/l, an operation does not entail the development of complications [18, 19].

A high bilirubinemia level requires measures that are mainly aimed at biliary decompression, resolution of the symptoms of OJ and its complications, and the prevention of a more severe hepatic insufficiency. Timely treatment of common bile duct diseases complicated by OJ is still a relevant issue with no definitive solution. Despite the use of mini-invasive interventions, the total serum bilirubin level significantly influences the outcomes and duration of biliary decompression. The introduction of antegrade endobiliary interventions in its turn somewhat facilitated direct access to bile ducts [20, 21].

However, there are still no precise recommendations concerning the duration of biliary decompression depending on the duration of OJ and baseline total serum bilirubin in benign and malignant common bile duct diseases complicated by OJ.

THE AIM

The aim of the study is to define the optimum duration of percutaneous transhepatic cholangiodrainage (PTCD) depending on the duration of obstructive jaundice (OJ) and baseline total serum bilirubin in patients with benign and malignant common bile duct diseases complicated by OJ.

MATERIALS AND METHODS

During the period from 2011 to 2017, 88 patients with benign and malignant common bile duct diseases complicated by obstructive jaundice underwent percutaneous transhepatic cholangiodrainage (PTCD) at the Surgery Department No. 1 of Kharkiv National Medical University at the clinic of State Institution "Zaycev V.T. Institute of General and Urgent Surgery of the National Academy of Medical Sciences of Ukraine". The causes of obstructive jaundice were the following diseases: choledocholithiasis in 6 patients (6.8%), common bile duct strictures in 2 (2.3%), biliodigestive anastomosis strictures in 7 (8%) and cholangiocarcinomas of various localization in 73 (82.9%) patients.

The patients' age varied between 33 and 88 years with the mean age being 65 years. There were 34 (38.6%) men and 54 (61.4%) women in both groups.

The patients were divided into three groups: the first group (1) included 15 patients (17.1%) with benign common bile duct diseases, the second group (2) included 11 patients (12.5%) with resectable cholangiocarcinomas, and the third group (3) included 62 patients (70.4%) with unresectable cholangiocarcinomas.

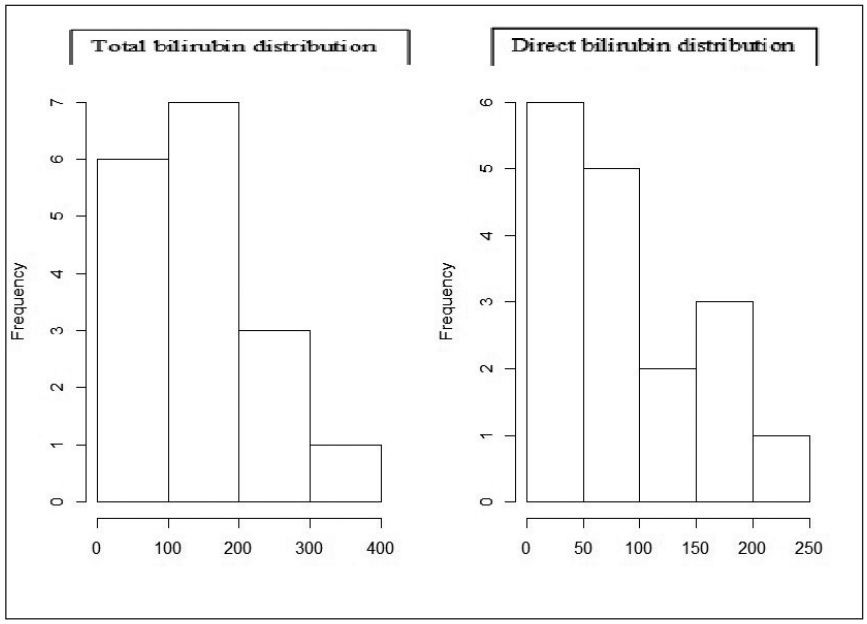

Fig. 1. Distributions of total and direct bilirubin after PTCD in Group 1 patients.

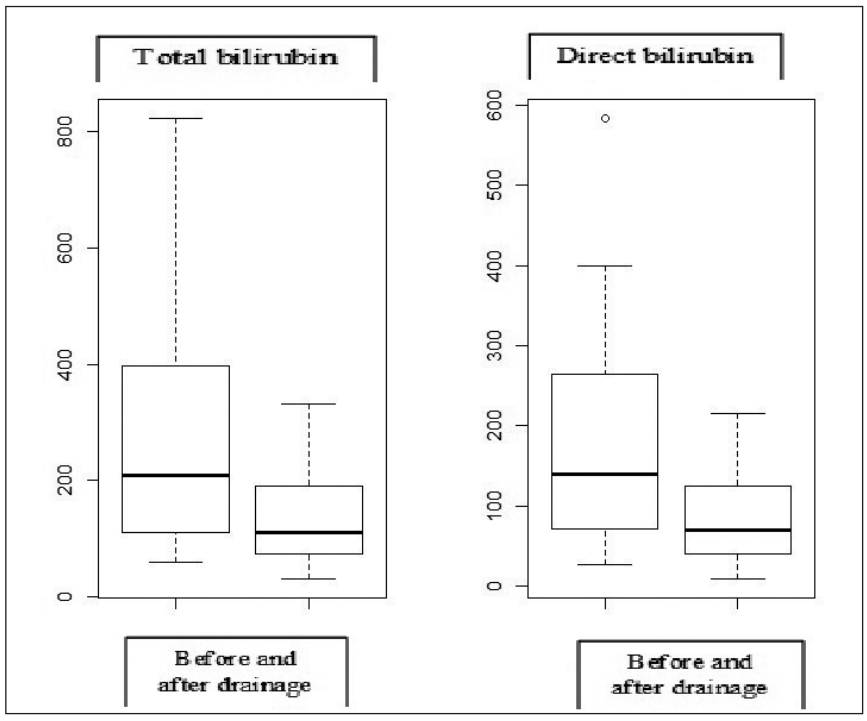

Fig. 2. Mean total and direct bilirubin before and after PTCD in Group 1 patients.

The duration of cholestasis was determined according to O.V. Smirnov's (1974) classification. Acute OJ was observed in 38 patients (43.2%), whereas acute prolonged and chronic OJ was observed in 11 (12.5%) and 39 (44.3%) patients, respectively.

The patients were distributed in terms of the total serum bilirubin level: 43-150 μmole/l –14 patients (15.9%), 150-250 μmole/l – 20 (22.7%), 250-400 μmole/l – 28 (31.8%), more than 400 μmole/l – 26 (29.6%) patients.

The study profile was in conformity with the CONSORT international requirements and had a respective study design of retrospective and prospective randomized clinical trial. The study was authorized by the ethical committee of Kharkiv National Medical University (meeting minutes No. 3 dated 03.04.2019). All ethical principles have been observed. Attached is the expert opinion regarding the authorization to publish materials in the press and other mass media. All patients gave an informed consent for their treatment results to be used for research purposes.

In order to determine optimum terms of biliary decompression using antegrade endobiliary interventions, namely PTCD, we decided to apply the Poisson process, and, to be more precise, the quasi-Poisson distribution that reflects the process of total serum bilirubin reduction [23, 24, 25, 26, 27, 28]. The latter reflects the duration of biliary decompression taking into account the variable

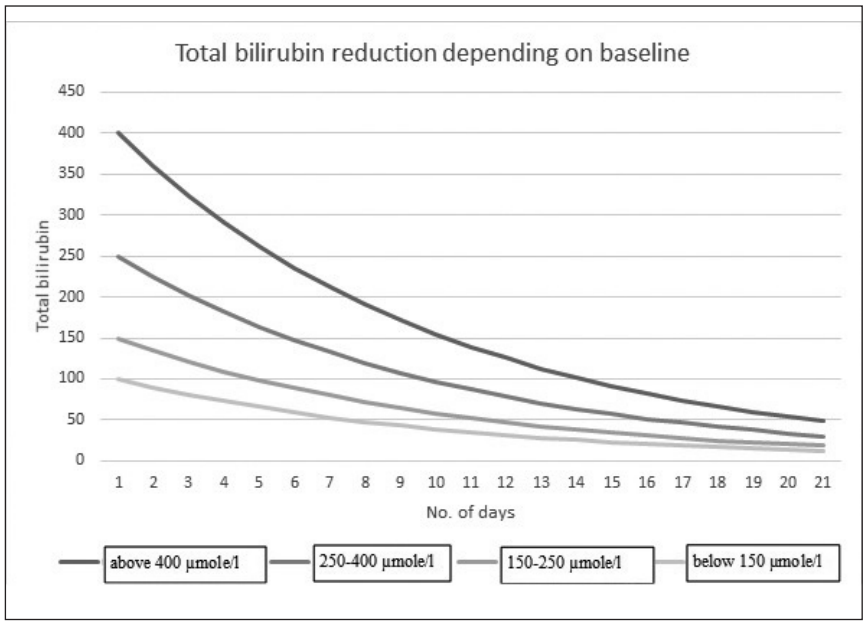

Fig. 3. Plots of total bilirubin reduction with time as compared to baseline in Group 1 patients.

– the bilirubin level after drainage with respect of time – whose value was log-transformed: **(log(total bilirubin/ duration of cholangiodrainage))**. The choice of the model for predicting the process of bilirubin reduction based on quasi-Poisson model is explained by the fact that the dispersion and the mean are equal in the Poisson distribution, whereas excessive dispersion was observed in our case. The distributions of total and direct bilirubin were checked against the difference of dispersion and the mean. The difference was significant, so a regression model based on quasi-Poisson distribution was selected for analysis. Using the R software environment, a regression model was built and regression equality coefficients were analyzed, which allowed us to determine mean durations of biliary decompression depending on OJ duration and total serum bilirubin level.

Statistical processing of digital data was performed on a personal computer using Excel 2010, SPSS and R – free statistical software. The representativeness of the findings were assessed based on the Mann-Whitney test, Student's t-test and the $\chi 2$ test, confidence intervals were calculated using the Clopper-Pearson method. The results were considered statistically significant at $p<0.05$.

RESULTS

Within the first two days after admission, all patients with benign and malignant common bile duct diseases underwent PTCD under X-ray or ultrasound navigation with the purpose of biliary decompression. Cholangiodrainage was inserted for 12 (13.6%) patients with moderately dilated intrahepatic ducts (<5 mm).

Subsequently, 16 (18.2%) patients underwent reconstructive-reparative surgeries, including 5 (5.7%) for choledocholithiasis, 11 (12.5%) for cholangiocarcinomas of various localization, and another 2 (2.3%) patients underwent mini-invasive interventions with combined antegrade and retrograde access in the case of "endoscopically complicated forms" of choledocholithiasis. In the rest of the patients, antegrade endobiliary interventions were the only treatment manipulation, including 8 (9.1%) patients with benign common bile duct diseases due to their sufficiency or a high anesthetic and operative risk and severity of comorbidities and 62 (70.4%) patients with unresectable cholangiocarcinomas.

The process of bilirubin reduction in Group 1 patients was considered to be changing according to a Poisson process [23-28]. In this group of patients, total bilirubin levels reduced with time as follows: average total bilirubin was 267.9 μmole/l before biliary decompression, and 139.24 μmole/l after treatment. The arithmetic mean of the difference is 128.7 μmole/l ($p<0.001$). Direct bilirubin decreased from 182.84 μmole/l to 87.55 μmole/l with the arithmetic mean of the difference being 95.3 μmole/l ($p<0.001$). However, the rate of total and direct bilirubin reduction is not linear as, in most cases, bilirubin significantly decreases during the first day, and the process slows down later.

The distribution of bilirubin levels after treatment for a sample population of patients demonstrates pronounced asymmetry. (Fig. 1 shows distributions of total and direct bilirubin, and Fig. 2 shows differences of means before and after PTCD).

The distributions of total and direct bilirubin in Group 1 patients were checked for the difference of dispersion and the mean. The difference was significant, so the quasi-Poisson distribution was selected for analysis [23-28].

The reduction rate also depends on OJ duration: the rate is higher for acute OJ and lower for acute prolonged jaundice, and on the baseline bilirubin level: the rate is higher at bilirubin levels of 250-400 μmole/l than at levels below 150 μmole/l. Therefore, in order to establish the correlation between the bilirubin level after PTCD and the number of drainage days, OJ duration and baseline bilirubin, a logarithmic function was applied rather than a linear one.

Table I. Recommended duration of biliary decompression for patients with benign common bile ducts diseases following PTCD

Baseline total bilirubin (μmole/l)	Duration of cholangiodrainage (days)
below 150 μmole/l	7-9
150-250 μmole/l	11-13
250-400 μmole/l	15-17
above 400 μmole/l	more than 20

On average, in Group 1 patients with chronic OJ and total bilirubin below 150 μmole/l, its final level was 25.5 μmole/l. Every day, total bilirubin will decrease by 10%. Thus, in case of baseline bilirubin level below 150 μmole/l, the reduction of bilirubin to this level will take 14 days.

If a patient's total bilirubin level is 150-250 μmole/l with chronic OJ, the final total bilirubin level will be 51.85 μmole/l after the same period of time as for the patients with a bilirubin level below 150 μmole/l. If a patient's total bilirubin level is 250-400 μmole/l, the mean bilirubin level after the first day after cholangiodrainage will be 62.24 μmole/l, and it will be 152.16 μmole/l at a level above 400 μmole/l. (Figure 3 shows plots of total bilirubin reduction with time as compared to baseline in Group 1 patients).

For patients with acute OJ, the total bilirubin level after PTCD is somewhat higher than for patients with a bilirubin level below 150 μmole/l (26.18 μmole/l), whereas it is somewhat lower for patients with acute prolonged OJ (16.12 μmole/l). However, the reduction rate for different forms does not essentially differ. The process of direct bilirubin reduction is the same as for total bilirubin.

Thus, based on the conducted analysis, the duration of PTCD-based biliary decompression that is optimum for patients with benign and malignant common bile duct diseases complicated by OJ was estimated. For these patients, the duration averaged 10-12 days since, irrespective of the baseline total bilirubin level, it decreases by an average of 10% per day. (Table I includes mean durations (number

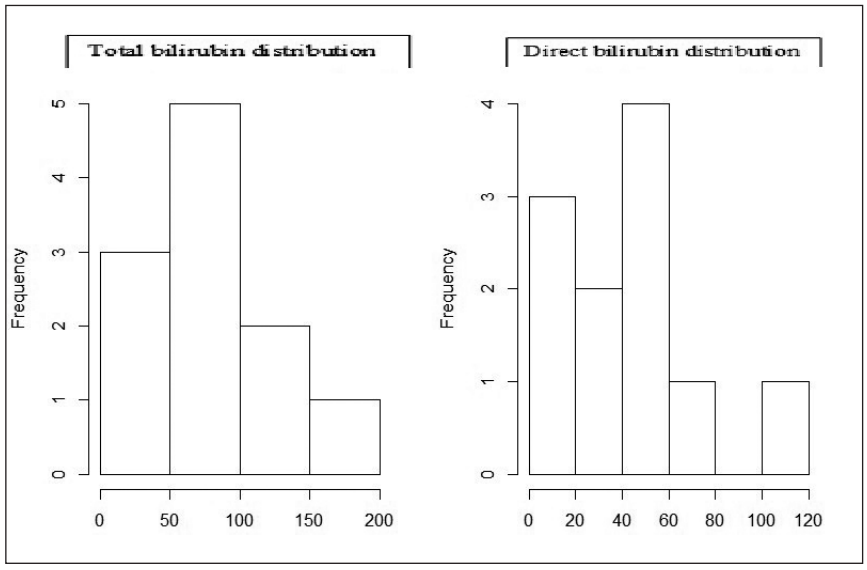

Fig. 4. Distributions of total and direct bilirubin after PTCD in Group 2 patients.

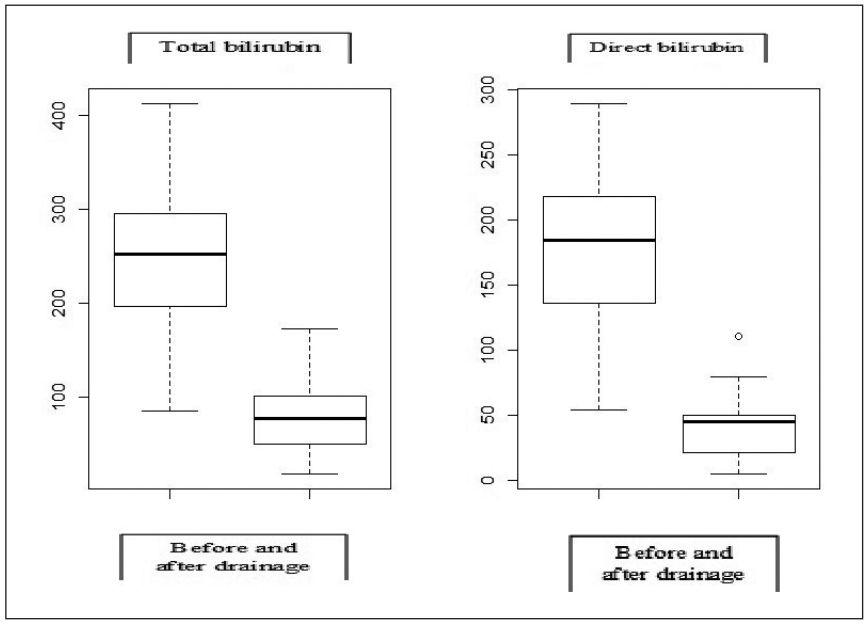

Fig. 5. Distribution of mean total and direct bilirubin before and after PTCD in Group 2 patients.

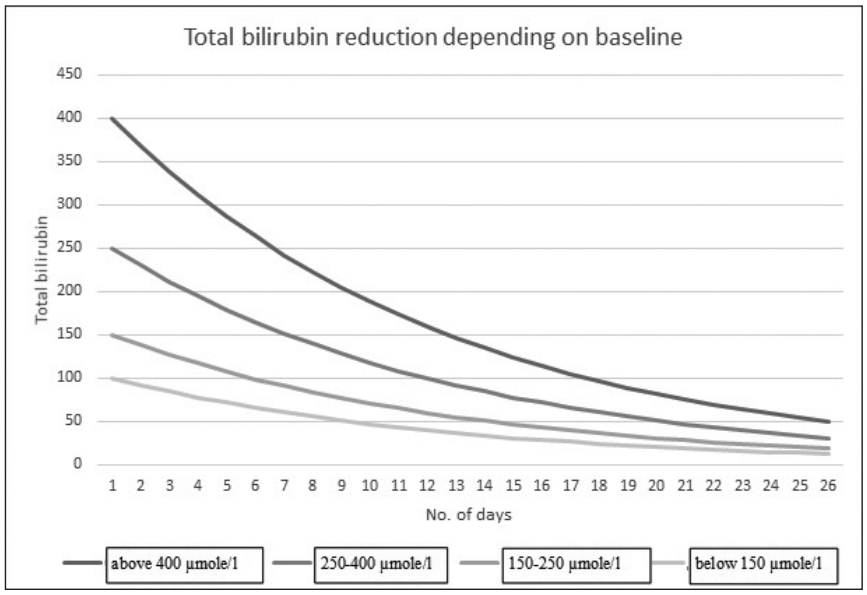

Fig. 6. Plots of total bilirubin reduction with time as compared to baseline in Group 2 patients.

of days) of PTCD that brings the bilirubin level below 50 μmole/l). However, it should be noted that total bilirubin should be controlled in the process of treatment, especially at the final stage.

The use of PTCD was analyzed in Group 2 patients. The process of total bilirubin reduction during biliary decompression using PTCD in Group 2 patients, just like in Group 1 patients, was considered to be changing according to a Poisson process [23-28].

In Group 2 patients, total bilirubin levels during biliary decompression reduced with time as follows: average total bilirubin was 243 μmole/l before treatment and 78.56 μmole/l after treatment. The arithmetic mean of the difference is 164.26 μmole/l with the difference being significant at $p<0.001$. Direct bilirubin decreased from 172.76 μmole/l to 44.22 μmole/l with the arithmetic mean of the difference being 128.55 μmole/l ($p<0.001$).

The distribution of bilirubin levels after treatment for patients from subgroup 2A demonstrates pronounced asymmetry. (Fig. 4 shows distributions of total and direct bilirubin, and Fig. 5 shows differences of means before and after PTCD).

The distributions of total and direct bilirubin in Group 2 patients were checked for the difference of dispersion and the mean. The difference was significant, so the quasi-Poisson distribution was selected for analysis [23-28].

On average, in Group 2 patients with chronic OJ and total bilirubin below 150 μmole/l, its final level was 8.35 μmole/l. Every day, total bilirubin will decrease by 8%. Thus, in case of baseline bilirubin level below 150 μmole/l, the reduction of bilirubin to this level will take 12 days.

If the total bilirubin level of a patient with chronic OJ is 150-250 μmole/l, the final total bilirubin level will be 23.38 μmole/l after the same period of time as for the patients with a bilirubin level below 150 μmole/l. If a patient's total bilirubin level is 250-400 μmole/l, the mean bilirubin level after the first day after cholangiodrainage will be 19.28 μmole/l, and it will be 26.3 μmole/l at a level above 400 μmole/l.

It was found that the total bilirubin level depends only on the duration of biliary decompression, and not on its baseline level. The difference between total bilirubin levels is not high, so the duration of PTCD will not differ significantly for Group 2 patients with different baseline levels. (Figure 6 shows plots of total bilirubin reduction with time as compared to baseline total serum bilirubin).

Total bilirubin after PTCD is somewhat higher for patients with acute OJ than for patients with total bilirubin below 150 μmole/l (8.76 μmole/l) and twice as high for patients with acute prolonged OJ (16.03 μmole/l). However, the reduction rate does not differ essentially depending on the duration of OJ. Therefore, total bilirubin should be controlled individually for each patient when performing biliary decompression. The reduction process of direct bilirubin is the same as for total bilirubin, but its reduction is somewhat faster; it was found however that the influence of OJ duration and baseline total bilirubin is not significant. (Table II shows recommended durations of biliary decompression using PTCD in resectable cholangiocarcinomas prior to a reconstructive-reparative operative intervention).

However, these values may be adjusted depending on the direct bilirubin reduction rate and be 2-3 days less since the reduction rate of direct bilirubin is somewhat lower than that of total bilirubin.

We have singled out a third group of patients who had knowingly unresectable common bile tumors and underwent PTCD as the only treatment manipulation or in combination with endobiliary stenting. These patients were divided into subgroups: patients with knowingly unresectable tumor processes who were inserted an external-internal PTCD – Subgroup 3A including 36 (58.1%) patients, and those who were inserted an external PTCD – Subgroup 3B including 26 (41.9%) patients.

The process of bilirubin reduction in Group 3 patients, just like in patients of two previous groups, is considered to be changing according to a Poisson process [23-28].

Table II. Recommended duration of biliary decompression using PTCD for patients with resectable cholangiocarcinomas

Baseline total bilirubin (μmole/l)	Duration of cholangiodrainage (days)
below 150 μmole/l	9-10
150-250 μmole/l	13-14
250-400 μmole/l	19-21
above 400 μmole/l	More than 25

In Subgroup 3A patients, total bilirubin levels reduced with time as follows: average total bilirubin was 324.17 μmole/l before treatment and 240.42 μmole/l after treatment. The arithmetic mean of the difference is 83.75 μmole/l with the difference being significant at p=0.001. Direct bilirubin decreased from 219.45 μmole/l to 161.76 μmole/l with the arithmetic mean of the difference being 62.67 μmole/l (p=0.001).

The distribution of total bilirubin levels after treatment for patients from subgroup 3A demonstrates pronounced asymmetry. (Fig. 7 shows distributions of total and direct bilirubin, and Fig. 8 shows differences of means before and after PTCD).

The distributions of total and direct bilirubin in Subgroup 3A patients were checked for the difference of dispersion and the mean using a quasi-Poisson distribution [23-28].

On average, in Subgroup 3A patients with chronic OJ and total bilirubin below 150 μmole/l, its final level was 20.76 μmole/l. Every day, total bilirubin will decrease by

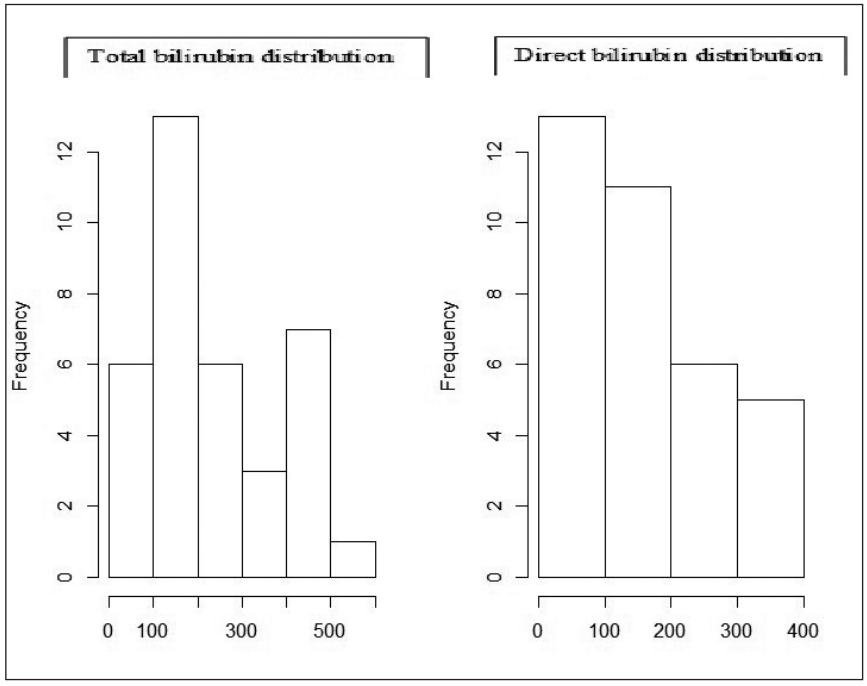

Fig. 7. Distributions of total and direct bilirubin after PTCD in Subgroup 3A patients.

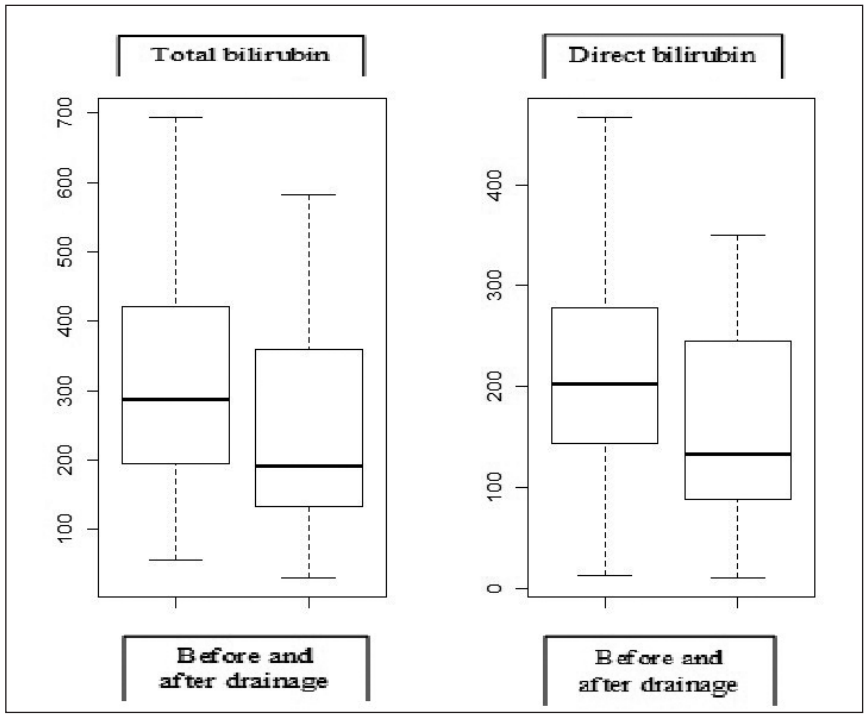

Fig. 8. Mean total and direct bilirubin levels before and after PTCD in Subgroup 3A patients.

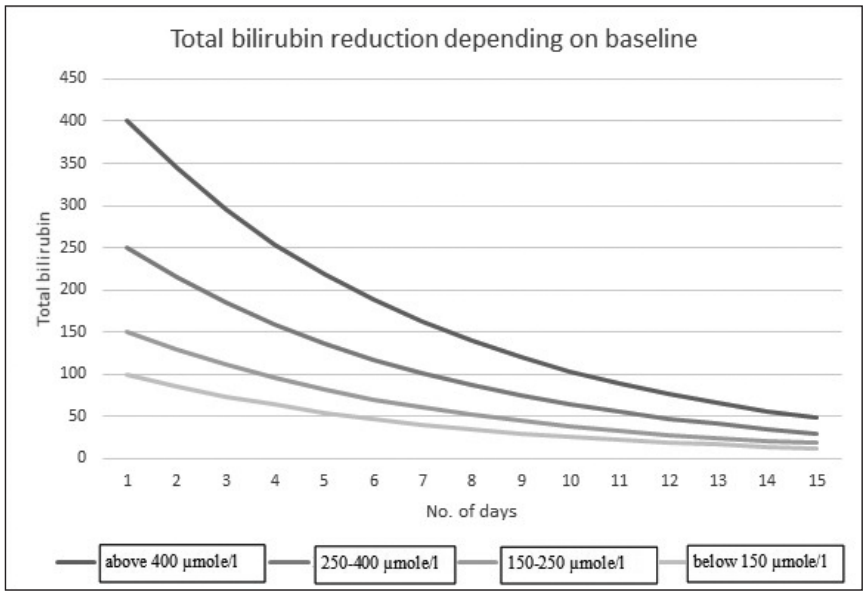

Fig. 9. Plots of total bilirubin reduction with time depending on baseline total bilirubin in Subgroup 3A patients.

14%. Thus, in case of baseline bilirubin level below 150 µmole/l, the reduction of bilirubin to this level will take around 12 days.

If the total bilirubin level of a patient with chronic OJ is 150-250 µmole/l, the final total bilirubin level will be 71.28 µmole/l after the same period of time as for the patients with a bilirubin level below 150 µmole/l. If a patient's total bilirubin level is 250-400 µmole/l, the mean bilirubin level after the first day after cholangiodrainage will be 120.75 µmole/l, and it will be 185.83 µmole/l at a level above 400 µmole/l. (Figure 9 shows plots of total bilirubin reduction with time depending on baseline total bilirubin in Subgroup 3A patients).

Total bilirubin after PTCD is somewhat higher for patients with acute OJ than for patients with total bilirubin below 150 µmole/l (17.92 µmole/l) or for patients with acute prolonged OJ (18.66 µmole/l). However, the reduction rate does not differ essentially depending on the duration of OJ. The reduction process of direct bilirubin is the same as for total bilirubin.

Thus, based on the conducted analysis, the optimum duration of biliary decompression for total bilirubin reduction through the insertion of an external-internal PTCD was estimated for patients with unresectable cholangiocarcinomas. For these patients, the duration averaged 7 days since, irrespective of the baseline total bilirubin level, it decreases by an average of 14% per day. (Table III includes mean durations of biliary decompression that brings the bilirubin level below 50 µmole/l). However, it should be noted that total bilirubin should be controlled in the process of biliary decompression, especially at the final stage.

The reduction of total bilirubin in Subgroup 3B patients was similar, total and direct bilirubin decreased by around 13-14% per day, but final bilirubin levels were somewhat higher than in Subgroup 3A patients after the same period of time (though the difference is not significant). (Figures 10-11 show distributions of total and direct bilirubin after PTCD and the difference between mean total and direct bilirubin before and after PTCD in Subgroup 3B patients. Figure 12 shows plots of total bilirubin reduction depending on its baseline level. Table IV provides recommended durations of biliary decompression through the insertion of an external PTCD for patients with unresectable cholangiocarcinomas).

For these patients, the mean duration of biliary decompression is 8 days since total bilirubin decreases by an average of 13-14% per day regardless of its baseline level.

DISCUSSION

Since no methods have been found in the available literature to determine the optimal duration of bile duct de-

Table III. Recommended duration of biliary decompression through the insertion of an external-internal PTCD for patients with unresectable cholangiocarcinomas

Baseline total bilirubin (µmole/l)	Duration of cholangiodrainage (days)
below 150 µmole/l	5-6
150-250 µmole/l	8-10
250-400 µmole/l	11-12
above 400 µmole/l	More than 15

Table IV. Recommended duration of biliary decompression through the insertion of an external PTCD for patients with unresectable cholangiocarcinomas

Baseline total bilirubin (µmole/l)	Duration of cholangiodrainage (days)
below 150 µmole/l	5-7
150-250 µmole/l	9-11
250-400 µmole/l	12-13
above 400 µmole/l	More than 16

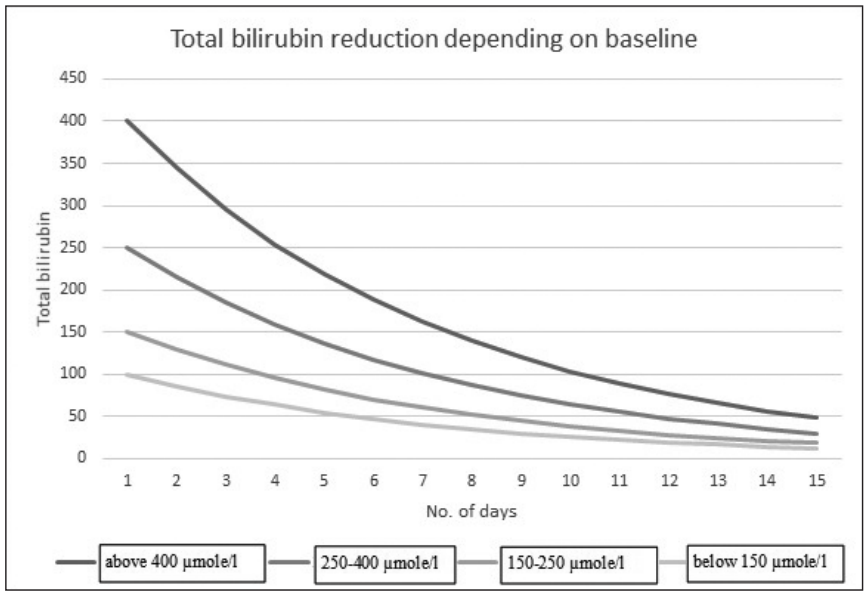

Fig. 10. Distributions of total and direct bilirubin after PTCD in Subgroup 3B patients.

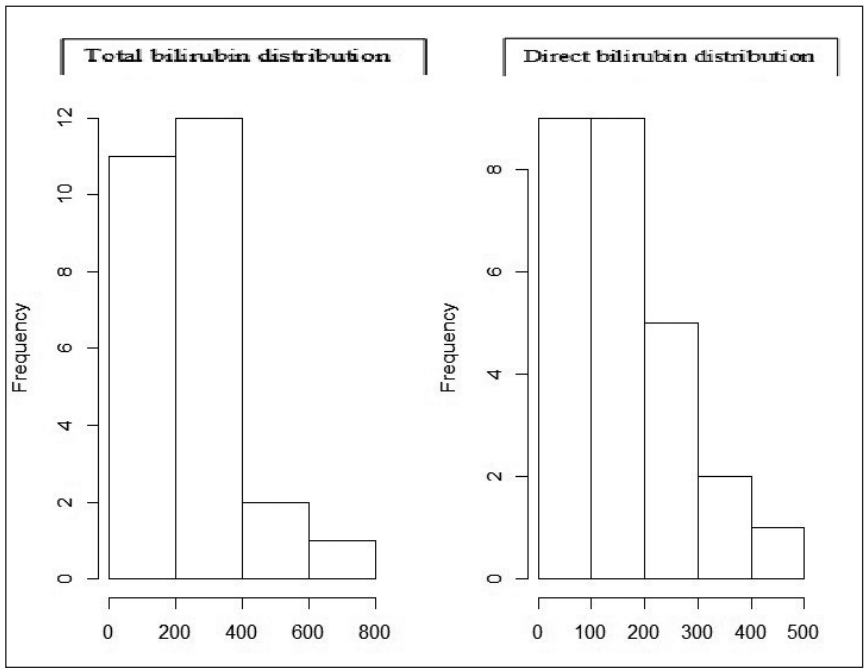

Fig. 11. Distributions of mean total and direct bilirubin levels after PTCD in Subgroup 3B patients.

compression, it was decided to apply the Poisson process, and, to be more precise, the quasi-Poisson distribution that reflects the process of total serum bilirubin reduction [23 - 28].

Found that the process of reducing serum total bilirubin is not linear but logarithmic function, which in turn causes first a rapid decrease in its level and then slow down the process of biliary decompression.

The use of the logarithmic function to determine the optimal timing of biliary decompression is also due to the fact that the process of reducing total serum bilirubin depends not only on its initial level but also on the duration of mechanical jaundice - the longer jaundice, the lower the rate of reduction of total bilirubin.

However, it should be noted that, for example, in patients with benign common bile duct diseases, in principle, the rate of decrease in total bilirubin does not differ depending on the duration of OJ. The process of reducing direct bilirubin is the same as the total. Regardless of the initial level of total bilirubin in patients with benign common bile duct diseases, the last one decreases by an average of 10% per day.

The process of reducing total bilirubin is somewhat slower in patients with resectable malignant common bile duct diseases, in whom PTCD is used as a preoperative preparation for reconstructive surgery - each day the bilirubin will be less by 8% than in the previous one. Because the duration of PTCD for patients with resectable malignant common bile duct diseases does not differ significantly depending on the initial level of total bilirubin and the duration of OJ, it is advisable to monitor the level of both total and direct bilirubin. It is determined that the process of reducing direct bilirubin is the same as the total, but its reduction is somewhat faster. This fact should be

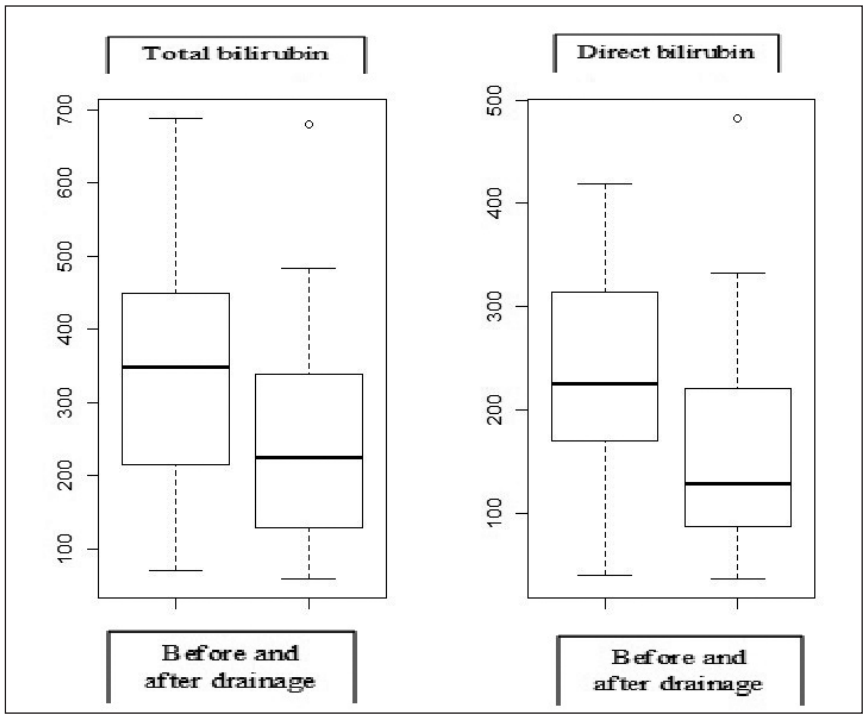

Fig. 10. Distributions of total and direct bilirubin after PTCD in Subgroup 3B patients.

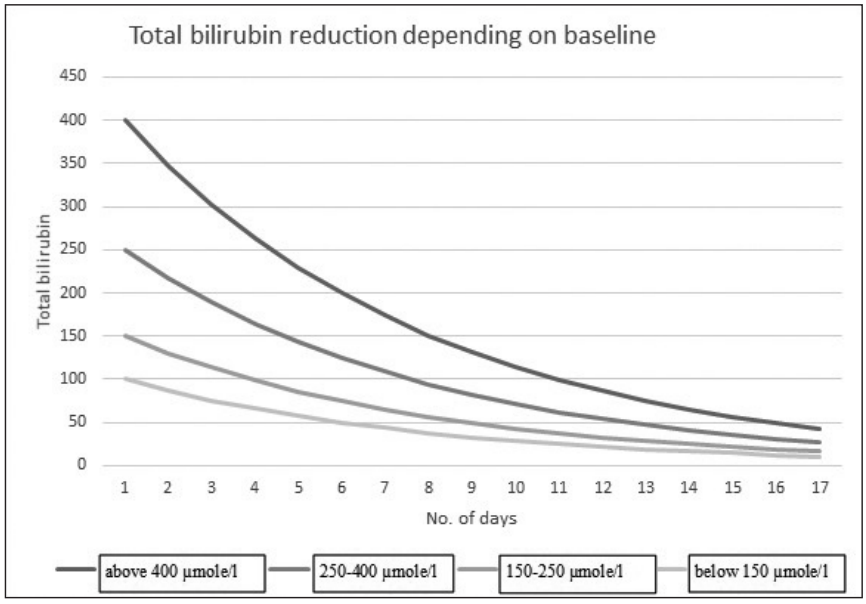

Fig. 12. Plots of total bilirubin reduction with time depending on baseline total bilirubin in Subgroup 3B patients

considered as under this term biliary decompression can be adjusted depending on the speed reduction of direct bilirubin and be less for 2-3 days.

The fastest rates of reduction of total bilirubin are in patients with unresectable malignant common bile duct diseases, in which the latter is reduced by 13-14% per day. In this category of patients, the rate of decrease in total bilirubin depending on the duration of OJ is not fundamentally different, but significantly depends on the initial level of total bilirubin. The process of reducing direct bilirubin is the same as total regardless of the type of PTCD, which in turn does not affect the duration of biliary decompression when using external-internal PTCD, which is physiological than external PTCD.

The developed prognostic model significantly increases the economic effect of the study, because with adequate setting and functioning of PTCD does not need to monitor the level of total serum bilirubin every day. It is advisable to focus on certain laboratory parameters at the final stage of biliary decompression in patients with common bile duct diseases complicated by mechanical jaundice.

CONCLUSIONS

Taking the above into consideration, it may be concluded that the process of total bilirubin reduction was the fastest in Group 3 patients. These patients take on average 8 days to reduce total bilirubin to the desired level, but the duration of biliary decompression depends significantly on baseline total bilirubin level.

The process is somewhat slower for Group 1 patients, but the final outcome also depends considerably on the

baseline total bilirubin level. The duration of biliary decompression for this category of patients is on average 10-12 days.

Group 2 patients need at least 12 days for biliary decompression, but the outcome does not significantly depend on baseline total bilirubin level and OJ duration. The direct bilirubin level needs to be constantly controlled in these patients.

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ORCID and contributionship:

Anastasiia L. Sochnieva: 0000-0003-0106-5247 [A, B, C, D, E, F]

Conflict of interest:

The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Anastasiia L. Sochnieva
Kharkiv National Medical University
4 Nauky Ave., 61000 Kharkiv, Ukraine
tel: +38099-770-75-20,
e-mail: sochnevanastya@gmail.com

Received: 19.10.2019
Accepted: 04.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

PERSONALITY TRAITS OF PATIENTS SUFFERING FROM PFO AND ASD AND INFLUENCE OF COVID-19 PANDEMIC TIME FOR PATIENTS SUFFERING FROM CONGENITAL HEART DEFECTS

DOI: 10.36740/WLek202009206

Adrianna Skoczek, Paweł Prochownik, Natalia Podolec, Urszula Gancarczyk, Piotr Podolec, Monika Komar
CLINICAL DEPARTMENT OF CARDIAC AND VASCULAR DISEASES WITH THE INTENSIVE CARDIAC SUPERVISION SUBDIVISION, INSTITUTE OF CARDIOLOGY, COLLEGIUM MEDICUM OF THE JAGIELLONIAN UNIVERSITY IN CRACOW, JOHN PAUL II HOSPITAL, COLLEGIUM MEDICUM OF THE JAGIELLONIAN UNIVERSITY IN CRACOW, CRACOW, POLAND

ABSTRACT

Introduction: The work presents a research project carried out in John Paul II Hospital in Cracow in Clinical Department of Cardiac and Vascular Diseases with the Intensive Cardiac Supervision Subdivision, with participation of 100 (50 F, 50 M) patients with congenital heart defects. The purpose of the work is to resolve the issue of personality specifics, and thus the different characteristics of people who suffer from congenital heart defects. Therefore, the following questions should be answered: Is there a relationship between personality traits and the occurrence of a congenital heart defect? What personality traits are characteristic for patients with congenital heart defects?

The aim: We aimed to assess personality traits of clients suffering from PFO and ASD. The article also talks about how coronavirus pandemic affects patients with congenital heart disease

Material and Methods: The research was conducted by psychologist Adrianna Skoczek. We performed a psychological clinical assessment and conducted the psychological tests like Eysenck Personality Questionnaire-Revised Short Version [EPQ-R(S)] and Eysenck's Impulsivity Inventory [IVE] by Hans J. Eysenck and Sybil G. Eysenck, the State-Trait Anxiety Inventory [STAI] by C. D. Spielberger, R. L. Gorsuch, R. E. Lushene describing personality traits of patients. Patients (F=50, M=50), with ASD (n=70) and with PFO (n=30).

Results: In people suffering from ASD, the level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking. In people suffering from PFO, a statistically significant difference was observed only between the level of psychoticism and other variables. The level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking, a statistically significant difference was found between the analyzed variables - anxiety as a trait and anxiety as a condition.

Conclusions: The results of the study allowed us to isolate the specific personality traits of patients suffering from congenital heart defects.

KEY WORDS: atrial septal defect; patent foramen ovale; personality traits; congenital heart defects, COVID-19

Wiad Lek. 2020;73(9 p. II):1926-1932

INTRODUCTION

PFO - patent foramen ovale - a persistent oval hole is a remnant of an oval hole located in the atrial septum. Blood circulation in utero takes place through: the umbilical vein, the venous line to the inferior vena cava, then the blood is led to the right atrium where, joining the blood from the superior vena cava, through the oval opening it leads to the left atrium of the fetus [1].

After delivery, due to the increase in pressure in the left atrium, the primary septum adheres to the secondary septum, which leads to narrowing of the oval opening channel, and then in most cases to close the opening. In about 25% of cases, the primary and secondary septa do not completely merge, which leads to the formation of a permanent oval hole [1].

ASD - atrial septal defect - a defect in the atrial septum causes blood leakage between the atria. ASD losses are divided into: ASDII - secondary hole type - occurs by approx. 80% of subjects - incorrectly developed secondary septum, ASDI - primary hole type - occurs in approx. 15% of subjects - pathological development and connection of endocardial cushions, svSD - main vein type - occurs in approx. 5% of patients - complete or partial septal defect is found between the main vein and right pulmonary veins, csASD - coronary sinus type - occurs in approx. 1% of patients - complete or partial hypoplasia of the coronary sinus wall adjacent to the left atrium [1].

THE AIM

To show personality traits typical of patients with congenital heart defects.

The following research hypotheses were adopted:

1. Extraversion is characteristic of people suffering from congenital heart disease PFO.
2. Psychoticism is not characteristic of people with ASD congenital heart disease.
3. Neuroticism is clearly the strongest characteristic of people with congenital heart disease PFO.
4. Impulsiveness is characteristic of people with ASD congenital heart disease.

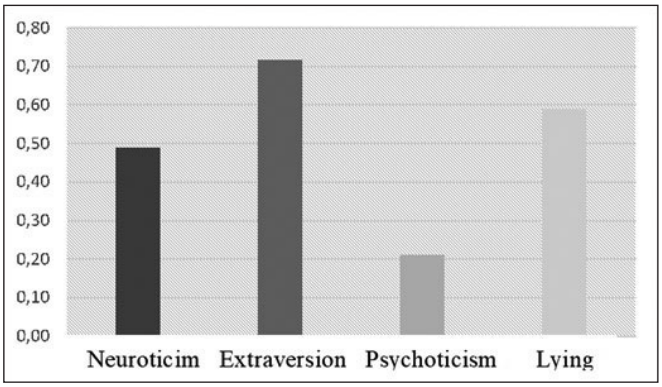

Fig. 1. The mean of the analyzed dimensions of the EPQ-R (S) tool Hans J. Eysenck and Sybil G. Eysenck for subjects with ASD defect
EPQ-R(S), Eysenck Personality Questionnaire-Revised Short Version, ASD, atrial septal defect

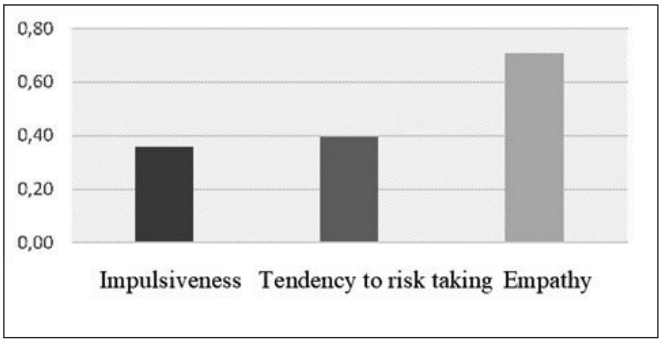

Fig. 2. Average of analyzed dimensions of IVE tool Hans J. Eysenck and Sybil G. Eysenck for subjects with ASD defect
IVE, Eysenck's Impulsivity Inventory, ASD, atrial septal defect

5. Tendency to risk-taking is not characteristic of patients suffering from ASD congenital heart disease.
6. Empathy is characteristic of people with PFO congenital heart disease.
7. Anxiety as a condition is characteristic of people suffering from ASD.
8. Anxiety as a trait is characteristic of people suffering from PFO.

MATERIAL AND METHODS

INFLUENCE OF COVID-19 PANDEMIC TIME FOR PATIENTS SUFFERING FROM CONGENITAL HEART DEFECTS

Each of the crises is associated with a negative impact on human mental health. Both patients who experienced various symptoms such as e.g. anxiety before the outbreak of the COVID-19 pandemic, and healthy people may deteriorate mental functioning [2].

The most important factors that affect the deterioration of a person's mental state during a pandemic are: isolation, lack of contact with loved ones, increasing domestic violence as well as a constant feeling of uncertainty about the future. In most countries, there are signs of depression as well as anxiety in

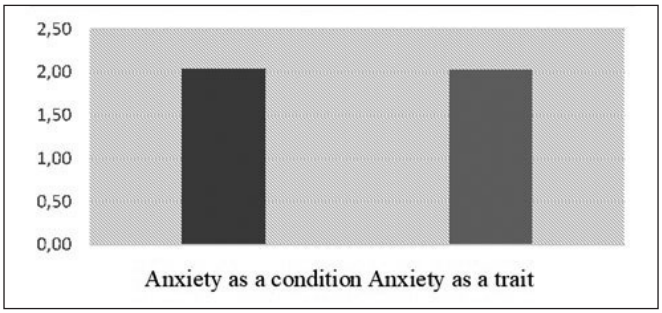

Fig. 3. Average of the analyzed dimensions of the STAI tool C. D. Spielberger, R. L. Gorsuch, R. E. Lushene for subjects with ASD defect
STAI, the State-Trait Anxiety Inventory, ASD, atrial septal defect

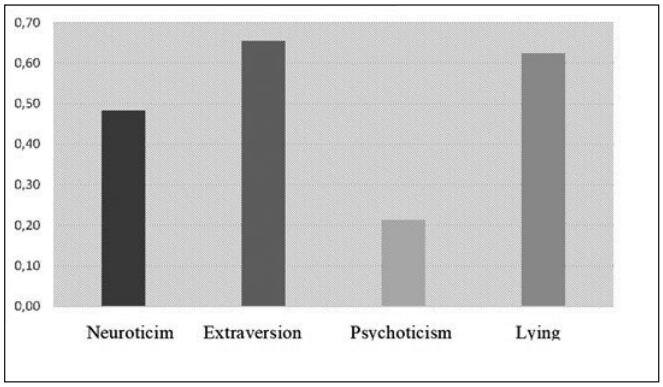

Fig. 4. Average of the dimensions of the EPQ-R (S) tool Hans J. Eysenck and Sybil G. Eysenck for subjects with a PFO defect.
EPQ-R(S), Eysenck Personality Questionnaire-Revised Short Version, PFO, patent foramen ovale

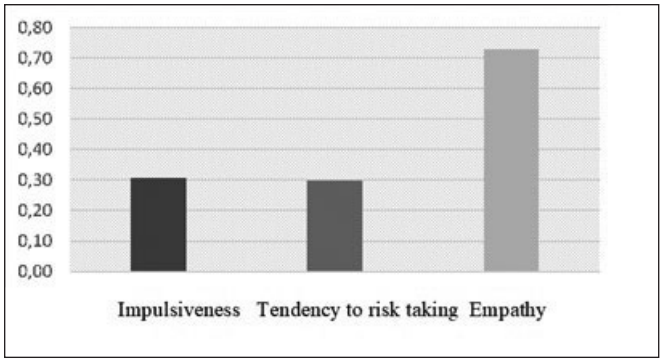

Fig. 5. Average of analyzed dimensions of IVE tool Hans J. Eysenck and Sybil G. Eysenck for subjects with PFO defect.
IVE, Eysenck's Impulsivity Inventory, PFO, patent foramen ovale

people healthy so far. The current pandemic situation directs people to reach for stimulants to reduce stress levels [2].

Research has been developed describing the level of extraversion associated with the current situation we are struggling with - COVID-19. People with a high level of extraversion were forced to increase social distance, which is very difficult for them. Higher conscientiousness results are associated with a lower tendency to violate recommendations [3].

People with cardiovascular disease (in particular, hypertension and coronary artery disease) have been shown to be at greater risk of COVID-19 infection. This

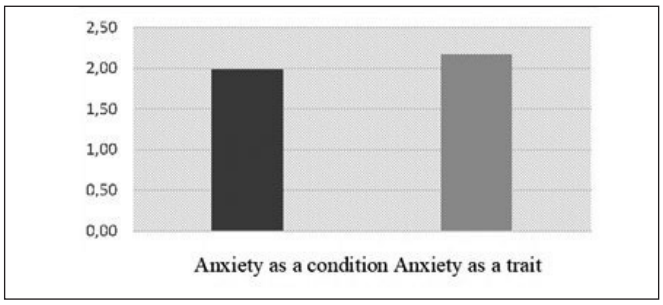

Fig. 6. The average of the analyzed dimensions of the STAI tool C. D. Spielberger, R. L. Gorsuch, R. E. Lushene for subjects with a PFO defect.
STAI, the State-Trait Anxiety Inventory; PFO, patent foramen ovale

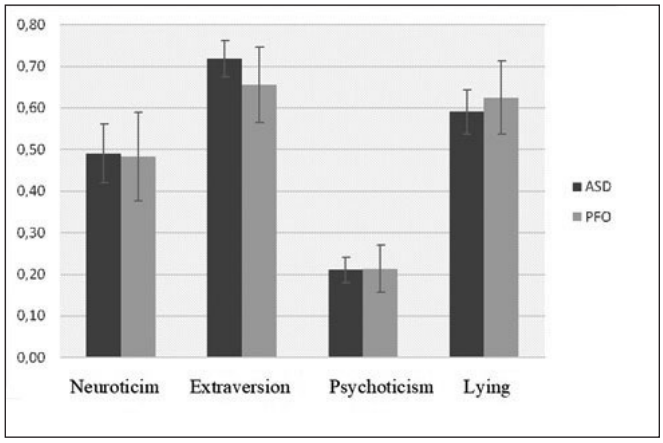

Fig. 7. Average levels of personality traits measured with the EPQ-R (S) tool Hans J. Eysenck and Sybil G. Eysenck, broken down by patients with ASD and PFO defects.
EPQ-R(S), Eysenck Personality Questionnaire-Revised Short Version, ASD, atrial septal defect; PFO, patent foramen ovale

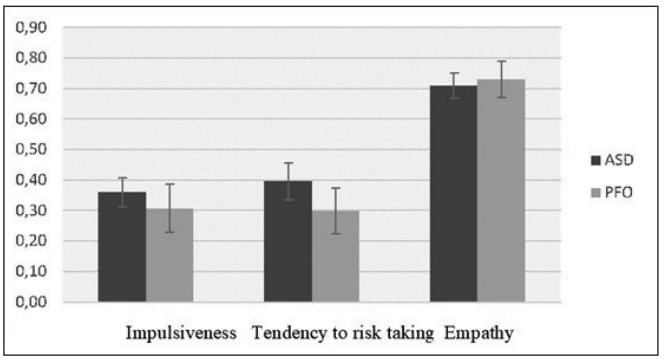

Fig. 8. Average levels of personality traits measured with the IVE tool Hans J. Eysenck and Sybil G. Eysenck, broken down by patients with ASD and PFO defects.
IVE, Eysenck's Impulsivity Inventory, ASD, atrial septal defect; PFO, patent foramen ovale

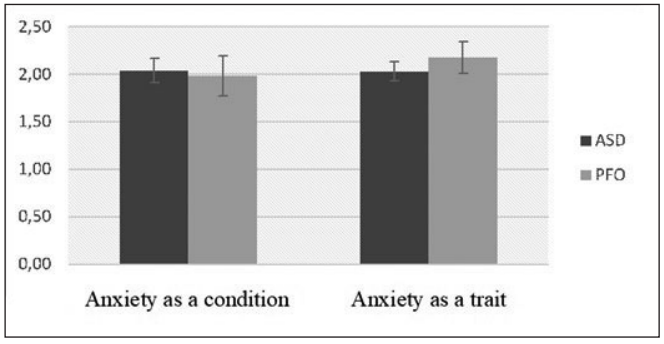

Fig. 9. Average levels of personality traits measured with the STAI tool C. D. Spielberger, R. L. Gorsuch, R. E. Lushene, broken down by patients with ASD and PFO defects.
STAI, the State-Trait Anxiety Inventory, ASD, atrial septal defect; PFO, patent foramen ovale

has often been associated with accelerated patient death. Unfortunately, to date, no studies have been developed regarding the exposure of people suffering from congenital heart defects [4].

Thus we still do not know how COVID -19 affects people with congenital heart defects, not only physically but also mentally. It is therefore important to research the effects of SARS-CoV-2 on patients with congenital heart defects. Other studies, in turn, showed that during a pandemic people show a lot of psychological conflicts between the desire to adhere to some rules in order to live in safety and the desire to maintain normality [5].

Recently, care for all patients, including cardiologic patients, has been significantly more difficult due to the coronavirus pandemic. Many patients with both ASD and PFO may feel disturbed by the lack of systematic contact with their attending physician, especially since the ailments caused by SARS-CoV-2 infection may resemble the already known cardiological ailments. The patient is not able to determine on his own what disease he can attribute to it, whether he has a heart defect or perhaps a coronavirus infection. COVID-19 is a disease caused by infection with the SARS-CoV-2 virus, involving the rapid spread of inflammatory processes in various organs. It attacks lungs as well as the cardiovascular system. It may have a different course in different patients. Approximately 20% of patients may have a severe course and these patients require hospitalization, intensive care and mechanical ventilation. About 1/5 -1/3 of hospital-treated patients have their cardiovascular system damaged, and about 40% of them die [6].

The site of entry of the SARS-CoV-2 virus is ACE 2 receptors that are found in the lungs, heart and kidneys. This virus then enters the endothelial cells, leading to their destruction. Damaged cells in the cardiovascular system initially cause microcirculation disorders, leading to vasoconstriction, which results in ischemia of many organs, intensification of inflammatory processes and hypercoagulability [6].

Common complications of SARS-CoV-2 infection are thrombophlebitis, acute coronary syndromes, myocarditis, acute heart failure as well as arrhythmias. Both arrhythmias and shortness of breath, chest pain, weakness, intolerance to physical exertion and swelling of the lower extremities can occur in PFO and ASD, as well as affect patients with these congenital heart defects and additionally infected with coronavirus. It should also be noted that drugs used to treat COVID-19 and complications such as antiviral drugs, chloroquine, hydroxychloroquine, azithromycin, antiarrhythmic and anticoagulant drugs also have proarrhythmic effects. In a study conducted in Wuhan, arrhythmias were seen in approximately 17% of

Table 1. The severity of personality traits measured with the EPQ-R (S) tool Hans J. Eysenck and Sybil G. Eysenck among those with ASD

Neuroticism		Extraversion		Psychoticism		Lying		F	p
M	SD	M	SD	M	SD	M	SD		
0,49	0,30	0,72	0,19	0,21	0,13	0,59	0,22	61,28	<0,001

M -mediana; SD - standard deviation; F - result of variance analysis; p - statistical significance
EPQ-R(S), Eysenck Personality Questionnaire-Revised Short Version, ASD, atrial septal defect

Table 2. The severity of personality traits measured by the IVE tool among subjects with ASD defect

Impulsiveness		Tendency to risk-taking		Empathy		F	p
M	SD	M	SD	M	SD		
0,36	0,20	0,40	0,26	0,71	0,17	58,97	<0,001

M -mediana; SD - standard deviation; F - result of variance analysis; p - statistical significance
IVE - Eysenck's Impulsivity Inventory, ASD - atrial septal defect

Table 3. Intensification of features measured with the STAI tool C. D. Spielberger, R. L. Gorsuch, R. E. Lushene among subjects with ASD defect

Anxiety as a condition		Anxiety as a trait				95% CI		
M	SD	M	SD	t	p	LL	UL	d Cohena
2,03	0,43	2,04	0,54	0,12	0,904	-0,11	0,13	0,02

M - mediana; SD - standard deviation; t - Student's t test result; p - significance; 95% CI - confidence interval for the difference between means; LL and UL - lower and upper limits of the confidence interval
STAI - the State-Trait Anxiety Inventory; ASD - atrial septal defect

Table 4. The severity of personality traits measured with the EPQ-R (S) tool Hans J. Eysenck and Sybil G. Eysenck among the subjects with PFO defect

Neuroticism		Extraversion		Psychoticism		Lying		F	p
M	SD	M	SD	M	SD	M	SD		
0,48	0,30	0,66	0,25	0,21	0,16	0,63	0,25	17,47	<0,001

M - mediana; SD - standard deviation; F - result of variance analysis; p - statistical significance
EPQ-R(S), Eysenck Personality Questionnaire-Revised Short Version, PFO, patent foramen ovale

Table 5. The severity of personality traits measured with the IVE tool Hans J. Eysenck and Sybil G. Eysenck among the subjects with PFO defect

Impulsiveness		Tendency to risk-taking		Empathy		F	p
M	SD	M	SD	M	SD		
0,31	0,22	0,30	0,21	0,73	0,17	44,41	<0,001

M -mediana; SD - standard deviation; F - result of variance analysis; p - statistical significance
IVE, Eysenck's Impulsivity Inventory; PFO, patent foramen ovale

Table 6. The severity of features measured with the STAI tool among those with a PFO defect

Anxiety as a condition		Anxiety as a trait				95% CI		
M	SD	M	SD	t	p	LL	UL	d Cohena
2,17	0,47	1,99	0,59	-2,44	0,021	-0,35	-0,03	0,34

N - number of observations; M - mediana; SD - standard deviation; t - Student's t test result; p - significance;
95% CI - confidence interval for the difference between means; LL and UL - lower and upper limits of the confidence interval
STAI - the State-Trait Anxiety Inventory, PFO - patent foramen ovale

patients in intensive care. This study did not analyze the type of arrhythmias. It should be noted that the factors predisposing to a more severe course of COVID-19 are male sex, advanced age, hypertension, diabetes, obesity, and cardiovascular diseases. Knowledge about the mechanisms causing a worse course COVID-19 in patients with cardiovascular disease is under investigation. Nevertheless, these patients require special care due to the limited access to healthcare services and medical procedures. The patients themselves also often seek help too late because of the pre-infection medicine. In studies conducted in Hong Kong during the SARS-2 epidemic, it was noted that from the time of onset of angina pain to the initiation of invasive treatment - primary percutaneous coronary angioplasty, PCI was about 3.5 times longer than the corresponding period of the previous year [6].

Table 7. The relationship between anxiety and personality traits measured with the STAI tool by C. D. Spielberger, R. L. Gorsuch, R. E. Lushene and IVE tool Hans J. Eysenck and Sybil G. Eysenck

		Anxiety as a condition	Anxiety as a trait
Impulsiveness	Pearson r	0,21	0,36
	Revelance	0,040	<0,001
Tendency of risk taking	Pearson r	-0,38	-0,30
	Revelance	<0,001	0,003
Empathy	Pearson r	0,22	0,27
	Revelance	0,031	0,007

STAI - the State-Trait Anxiety Inventory;
IVE - Eysenck's Impulsivity Inventory;

Table 8. The relationship between anxiety and personality traits measured with the STAI tool by C. D. Spielberger, R. L. Gorsuch, R. E. Lushene and EPQ-R (S) Hans J. Eysenck and Sybil G. Eysenck

		Anxiety as a condition	Anxiety as a trait
Neuroticism	Pearson r	0,40	0,51
	Revelance	<0,001	<0,001
Extraversion	Pearson r	-0,15	-0,22
	Revelance	0,151	0,027
Psychoticism	Pearson r	0,11	0,16
	Revelance	0,275	0,115
Lying	Pearson r	-0,08	-0,16
	Revelance	0,461	0,123

EPQ-R(S) - Eysenck Personality Questionnaire-Revised Short Version
STAI - the State-Trait Anxiety Inventory;

Table 9. Relationship of personality traits measured with IVE tools Hans J. Eysenck and Sybil G. Eysenck and EPQ-R (S) Hans J. Eysenck and Sybil G. Eysenck

		Impulsiveness	Tendency to risk-taking	Empathy
Neuroticim	Pearson r	0,53	-0,23	0,39
	Revelance	<0,001	0,019	<0,001
Extraversion	Pearson r	0,09	0,19	0,06
	Revelance	0,362	0,056	0,547
Psychoticism	Pearson r	0,27	0,06	-0,16
	Revelance	0,006	0,526	0,121
Lying	Pearson r	-0,36	-0,37	0,00
	Revelance	<0,001	<0,001	0,968

EPQ-R(S) - Eysenck Personality Questionnaire-Revised Short Version
IVE - Eysenck's Impulsivity Inventory;

Therefore, on April 21, 2020, European Society of Cardiology (ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic) guidelines have been published which aim to provide appropriate care to this group of patients. Also other societies around the world such as the Canadian Association of Interventional Cardiology, American College of Cardiology's (ACC), Interventional Council and Society of Cardiovascular Angiography and Intervention (SCAI), Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship (SCAI ELM) Members and Graduates, Peking Union Medical College Hospital have developed guidelines for the management of patients with STEMI and NSTEMI myocardial infarction depending on the coexistence of COVID-19 [6].

According to the aforementioned guidelines, patients requiring further diagnosis or invasive treatment were divided into groups defining the need for urgent or postponed medical procedures. For example, in patients with ASD or PFO, closure of the defect in the atrial septum, obstruction of the oval opening should be performed in the planned mode, i.e. it can be postponed for at least 3 months [6].

STATISTICAL DEVELOPMENT OF RESEARCH RESULTS

Statistical tests were performed using IBM SPSS Statistics version 25 to test the hypotheses set out in the study. With its help, frequency analysis, analysis of basic descriptive statistics together with the Kolmogorov-Smirnov distribution normality test, Pearson r correlation analysis, variance analysis in intra-group schemas, Mann-Whitney U tests for independent samples and Student's t tests for dependent and independent samples were performed.

CONGENITAL HEART DISEASE ASD AND PERSONALITY TRAITS OF PEOPLE SUFFERING FROM IT

In order to verify the next hypothesis, analogous analyzes of personality traits were carried out among subjects with ASD congenital heart disease. First, an analysis of the variance of results obtained by this group of subjects on the scales of the EPQ-R (S) tool [7]. Due to violation of the assumption about the sphericity of variables, the Greenhouse-Geisser correction was applied in reporting the result of the analysis. The test result turned out to be statistically significant - $F(2.20; 151.53) = 61.28$; $p < 0.001$; $\eta 2 = 0.47$. The eta value of the square indicates that the observed effect is strong. In order to check the essence of this effect, a post hoc analysis (with Bonferroni correction) was carried out. The only insignificant difference in the analyzed case is that between levels of neuroticism and the scale of lying. The averages described are presented in Table 1 and Figure 1.

Then, an analogous analysis of the variance of results obtained on the IVE scales was carried out [8]. Due to violation of the assumption about the sphericity of variables, the Greenhouse-Geisser correction was applied in reporting the result of the analysis. The test result turned out to be statistically significant - $F(1.68; 115.68) = 58.97$; $p < 0.001$; $\eta 2 = 0.46$. The eta value of the square indicates that the observed effect is very strong. In order to check the essence of this effect, a post hoc analysis (with Bonferroni correction) was carried out. The level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking. The difference between impulsiveness and tendency to risk-taking turned out to be statistically insignificant. The values of the discussed averages and the result of the analysis of variance are presented in Table 2 and Figure 2.

Then the Student's t-test analysis for repeated measurements was performed. The results obtained by the subjects with ASD defect were compared on the scales of the STAI tool [9].

Based on the results presented in Table 3, no statistically significant differences were found between the analyzed variables. The compared means are illustrated in Figure 3.

CONGENITAL HEART DISEASE PFO AND PERSONALITY TRAITS OF PEOPLE SUFFERING FROM IT

In order to verify the next hypothesis, analogous analyzes were carried out, but among those with a PFO defect. First, an analysis of the variance of results obtained by this group of subjects on the scales of the EPQ-R (S) tool was carried out [7]. The test result proved to be statistically significant - $F(3; 87) = 17.47$; $p < 0.001$; $\eta 2 = 0.38$. The eta value of the square indicates that the observed effect is strong. In order to check the essence of this effect, a post hoc analysis (with Bonferroni correction) was carried out. A statistically significant difference was observed only between the level of psychoticism and other variables. The discussed averages are presented in Table 4 and Figure 4.

Then, an analogous analysis of the variance of results obtained on the IVE scales was carried out [8]. The test result turned out to be statistically significant - $F(2, 58) = 44.41$; $p < 0.001$; $\eta 2 = 0.61$. The eta value of the square indicates that the effect observed is very strong. In order to check the essence of this effect, a post hoc analysis (with Bonferroni correction) was carried out. The level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking. The difference between impulsiveness and tendency to risk-taking turned out to be statistically insignificant. The values of the discussed means and the result of the analysis of variance are presented in Table 5 and Figure 5.

Then the Student's t-test analysis for repeated measurements was performed. The results obtained by the subjects with PFO defect were compared on the scales of the STAI tool [9].

Based on the results presented in Table 6, a statistically significant difference was found between the analyzed variables. The compared means are illustrated in Figure 6.

INFLUENCE OF THE TYPE OF HEART DEFECT ON PERSONALITY TRAITS

To verify the next hypothesis, a series of Mann-Whitney U tests were conducted. A nonparametric test was used due to a clear violation of the assumption about the equivalence of the compared groups. First, the influence of the type of heart defect on personality traits measured with the tool EPQ-R (S) [7]. The test result turned out to be statistically insignificant in the case of neuroticism ($p = 0.940$), extraversion ($p = 0.349$), psychoticism ($p = 0.917$) and the scale of lying ($p = 0.348$). The compared means are illustrated in Figure 7.

Then Mann-Whitney U tests were carried out for independent samples comparing the levels of severity of traits measured with the STAI tool [9] in the group with ASD and PFO defects. The test result was insignificant in the case of differences in the levels of impulsiveness ($p = 0.190$), tendency to risk-taking ($p = 0.104$) and empathy ($p = 0.639$). The compared means are illustrated in Figure 8.

Then Mann-Whitney U tests were carried out for independent samples comparing the levels of severity of traits measured with the STAI tool [4] in the group with ASD and PFO defects. The test result was insignificant in the case of the difference in levels of anxiety as both a condition ($p = 0.399$) as well as as traits ($p = 0.194$). The compared means are illustrated in Figure 9.

In addition, a series of Pearson r correlations were made between the scales used in the study of tools. First, the

results on the IVE scales were compared with [8] and STAI tool [9]. Based on the results presented in Table 1-6, statistically significant correlations were found between all variables. The results on the anxiety scale as a state correlate positively, weakly with the results on the impulsiveness and empathy scales. This means that as the results on the anxiety scale as a state increase, the results on the impulsiveness and empathy scales increase. A statistically significant, moderate but negative correlation with results on the tendency to risk-taking scale was found in the relationship between anxiety as a condition and tendency to risk-taking. This means that as results on the anxiety scale increase as a result, the results on the tendency to risk-taking scale decrease. In the case of results on the anxiety scale as a feature, statistically significant correlations were found with the results on all scales of the IVE tool [8]. In the case of the relationship with impulsiveness, it is positive and moderate, and empathy is positive, but weak. In the case of the relationship between the results on the anxiety scale as a feature and the results on the tendency to risk-taking scale, a statistically significant, moderate, but negative relationship was also observed (Table 7-9).

ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Bioethics Commission of Jagiellonian University in Cracow (No. 1072.6120.132.2017 from 28th September 2017) and informed consent was taken from all the patients. All patients agreed to the examination (part of the studies completed before the surgery, some after the surgery). Patients expressed willingness to participate in the operation, and the study submitted reported and approved by the bioethics committee. The study involved completing three psychological tests (EPQ-R(S), IVE, STAI) examining the personality structure and level of anxiety. This article does not contain any studies with human participants performed by any of the authors. This article does not contain any studies with animals performed by any of the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

DISCUSSION

In people suffering from ASD, the only insignificant difference in the analyzed case is that between levels of neuroticism and the scale of lying. The level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking. The difference between impulsiveness and tendency to risk-taking turned out to be statistically insignificant. Based on the results, no statistically significant difference was found between the analyzed variables - anxiety as a trait and anxiety as a condition.

In people suffering from PFO, a statistically significant difference was observed only between the level of psychoticism and other variables. The level of declared empathy was statistically significantly higher than the levels of impulsiveness and tendency to risk-taking. The difference between impulsiveness and tendency to risk-taking turned out to be statistically insignificant. Based on the results, a statistically significant difference was found between the analyzed variables - anxiety as a trait and anxiety as a condition.

CONCLUSIONS

The results of the study allowed us to isolate the specific personality traits of patients suffering from congenital heart defects.

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ORCID and contributionship

Adrianna Skoczek - 0000-0002-3952-9660 [A-F]
Paweł Prochownik - 0000-0002-6957-3590 [B-F]
Natalia Podolec - 0000-0003-0192-7310 [B,F]
Urszula Gancarczyk - 0000-0003-2283-3356 [B,E, F]
Piotr Podolec - 0000-0001-6101-2935 [A,D-F]
Monika Komar - 0000-0001-5341-2947 [A-F]

Acknowledgments
We would like to thank everyone who contributed to this work, the Director of the Hospital, John Paul II Hospital, The Clinical Department of Cardiac and Vascular Diseases with the Intensive Cardiac Surgeon Division Institute of Cardiology, and Collegium Medicum of the Jagiellonian University in Cracow, heads of Departments, as well as the Bioethics Committee, and in particular patients who did not refuse the examination.

Conflict of interest
Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Adrianna Skoczek
Baczków 210, Zakatek Street, 32-708 Baczków, Poland
phone number +48 790706725
e-mail: adriannaskoczek@gmail.com

Reseived: 15.07.2020
Accepted: 10.09.2020

ORIGINAL ARTICLE

VASCULAR ANOMALIES IN NEWBORNS: CLINICAL PRESENTATION, COMPLICATIONS, AND PECULIARITIES OF THERAPY

DOI: 10.36740/WLek202009207

Iryna M. Benzar[1], Anatolii F. Levytskyi[1], Daria S. Diehtiarova[1], Larysa Ya. Fedoniuk[2], Yaroslav S. Stravskyy[2], Daria A. Merkulova[3], Petro A. Sas[2]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

[2]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

[3]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: to analyze cases of vascular anomalies in newborns retrospectively to study their main clinical signs and to determine indications for urgent treatment.

Materials and methods: A retrospective review of 281 pediatric vascular anomalies diagnosed between 2011 and 2019 was performed. The results of clinical examination, prenatal history, laboratory, sonography, and radiological data were evaluated.

Results: Clinical manifestations in the newborn period documented in 170 (60.5%) patients, anomalies were visualized prenatally in 8.9% cases. Five newborns with head and neck LMs required urgent treatment, which amounted 7.9% of all newborns with LMs. The indication for urgent surgery was acute respiratory failure. Partial malformation resection with tracheostomy was performed to those patients, along with intraoperative injection of sclerotherapeutic agents and argon coagulation of residual malformation tissues. EXIT procedure was performed in one case. No correlation (p=0.2) was found between the number of skin lesions and the severity of liver lesions in children with multifocal hepatic hemangiomas, congestive cardiac failure suddenly occurs in one patient in the third week of life. Two newborns with diffuse hepatic hamangioma were manifested right after the birth with clinical signs of liver failure, hypothyreosis, and cardiac failure. Short courses of corticosteroids performed in 7 patients with KHE and Kasabach-Merritte fenomemn for thrombocytopenia correction.

Conclusions: Clinical signs of vascular anomalies in neonatal period were seen in 57.5% children with vascular anomalies, and only 2.9% of them required treatment. Treatment itself is advantageous only in cases when life-threatening complications develop, such as airways obstruction, cardiac and/or liver failure, thrombocytopenia.

KEY WORDS: vascular anomalies, vascular malformations, congenital and infantile hemangioma, newborns

Wiad Lek. 2020;73(9 p. II):1934-1939

INTRODUCTION

According to renewed International Society for the Study of Vascular Anomalies (ISSVA) 2018 classification, all vascular anomalies are divided into two basic groups: vascular malformations and vascular tumors [1].

Mentioned anomalies are fundamentally different not only by their anatomical, histological and pathophysiological features, but also by clinical course. This fact places a special emphasis on the importance of clear division of these two groups to choose the appropriate treatment tactics [2].

Dichotomous division to vascular tumors and vascular malformations was originally proposed in 1982 [3], and this basic principle is kept in modern classification. Along with that, knowledge of vascular anomalies has considerably improved through following decades [4, 5]. Genetic risk loci for many of them were determined, new nosological units were described, numerous mechanisms pathogenesis were discovered, and new treatment methods were implemented. In earlier publications for instance it was suggested that the basic pathogenetic causes of lymphatic malformations (LMs) were disorders in embryological development of lymphatic vessels with following absence of lymphatic channels and venous vessels communications [6]. In recent publications arguments are provided for LMs are not the result of vasculogenesis defects but of sporadic genetic abnormalities in specific cells [7] that will create a possibility of target therapy.

Despite modern medical science achievements, there are issues of diagnostic and treatment tactics of vascular anomalies in newborns, as typical clinical presentation is not always seen, there is little data about ongoing course of disease and limitations for additional invasive methods of examination.

THE AIM

Aim of the study was to analyze clinical cases of vascular anomalies in newborns retrospectively to study their main clinical signs and to determine indications for urgent treatment.

MATERIALS AND METHODS

A retrospective study was conducted to review the medical documents of 281 pediatric patients with vascular anomalies.

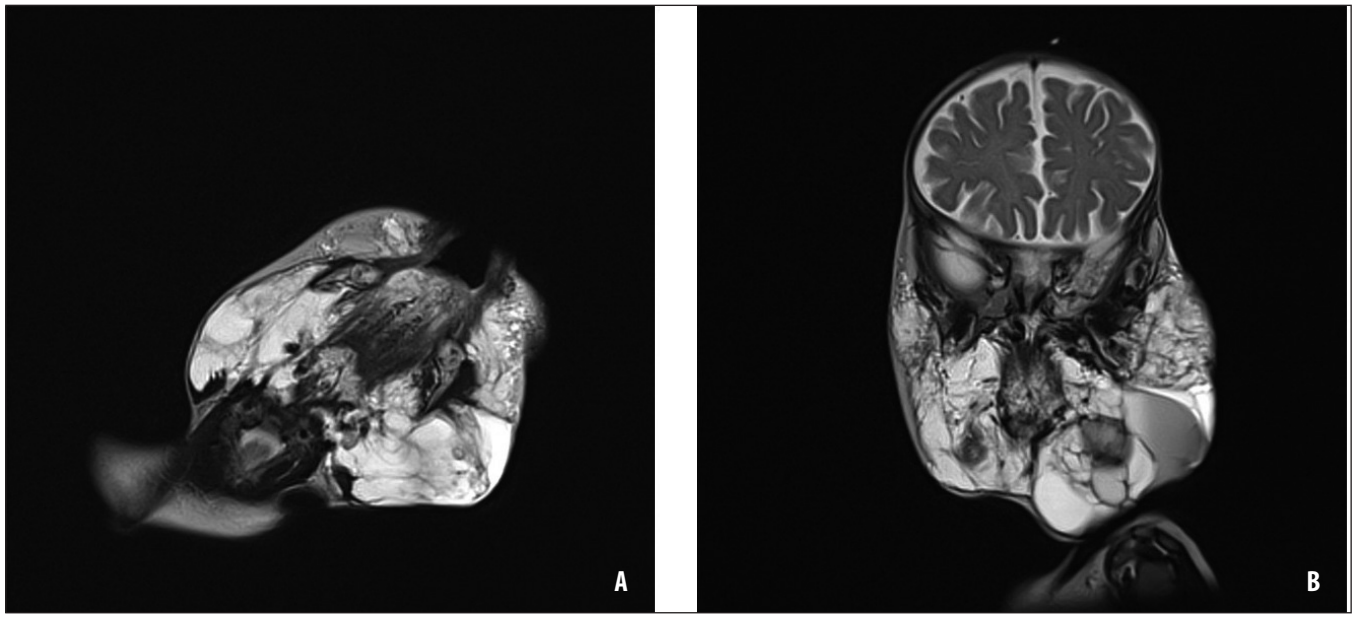

Fig. 1. Newborn male with head and neck LM. Axial (A) and coronal (B) T2-weighted MRI showing diffuse infiltrative affection of all tissues by macro- and microcystic mass.

The diagnosis and treatment of all cases were performed in one hospital in a period from January 2011 to December 2019. The group of patients aged 0-28 days (newborns) with symptoms of vascular anomalies was selected. The results of clinical examination, prenatal history, laboratory, sonography, computed tomography (CT) and magnetic resonance imaging (MRI) data were evaluated. Where possible, histological confirmation was included. Vascular malformations were diagnosed in 198 (70.5%) and vascular tumors in 83 (29.5%) children. Distribution of vascular malformations was as follows: LMs were diagnosed in 145 (73.2%) children, venous malformations (VMs) - in 39 (19.7%) and arteriovenous malformations (AVMs) in 14 (7.1%) patients. Among 83 patients with vascular tumors infantile hemangioma (IH) was predominant, diagnosed in 68 (81.9%) children, congenital hemangioma (CH) - in 9 (10.9%) and kaposiform hemangioendotheliomas (KHE) in 6 (7.2%) patients. A detailed analysis of clinical cases was performed to determine those 170, where clinical presentation appeared at the age of 0-28 days. The results of fetal sonography were available in 180 patients, and there was one fetal MRI.

The statistical analysis was performed using IBM SPSS Statistics, version 23. The data is presented as an average of 95 percent confidence interval or standard deviation. The qualitative data were analyzed in a univariate analysis, with the Pearson's correlation coefficient. Independent predictors of morbidity in newborn patients were determined using multivariable logistic regression analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

Clinical manifestations of vascular anomalies in the newborn period documented in 170 (60.5%) patients, anomalies were visualized prenatally in 8.9% cases. Among 145 children with LMs clinical signs were detected in neonatal period in 78 (53.8%) cases. 19 (24.4%) of them were diagnosed prenatally. The most common were head and neck LMs – 63 (80.8%) patients. Less frequently LMs were seen in axilla (n=8; 10,3%) either in pelvis and extremities (n=7; 8.9%). The first clinical sign of cystic LMs was disfigurement owing to a mass in affected anatomical regions. Complications were registered in 17 (27.0%) children with head and neck LMs, including in particular upper airways compression followed by acute respiratory failure (n=5, 6.4%), transitory stridor (n=8, 12.7%), transitory dysphagia (n=2; 3.2%), intermittent lymphorrhea in children with affection of oral mucosa (n=2, 3.2%). Five newborns with head and neck LMs required urgent treatment, which amounted 6.4% of all newborns with LMs. MRI showed that mass is represented by cysts of different diameters and multiple septa, with average size of 301,05±56,28 sm^2, that affect head and neck tissues on both sides and spread beyond fascial leaves (Fig.1). The sizes of LMs in this group of patients were almost double the average of 153.0±114.2 sm^2 ($p < 0.05$).

The indication for urgent surgery was clinical presentation of acute respiratory failure, caused by disorders in respiration mechanics and external obstruction of upper airways. Partial malformation resection with tracheostomy was performed to those patients, along with intraoperative injection of sclerotherapeutic agents (OK-432, bleomycin) into cysts' cavities and argon coagulation of residual malformation tissues. EXIT procedure (ex-utero intrapartum treatment) was performed in one case – trachea was intubated within a delivery room under preserved placental blood circulation in a baby with prenatally diagnosed head and neck LM with upper airways compression. On the tenth day of life the tracheostomy was performed with following sclerotherapy.

Clinical signs of VMs could be seen since the moment of birth in 18 out of 39 children (46,2%) and AVMs in 3 out of 14 (21,4%). The signs of VMs were skin lesions and superficial soft-tissue masses. AVMs presented with capillary spots. None of patients out of this group was diagnosed malformation during the first month of life, they all were referred to our clinic later with a provisional diagnosis of "hemangioma". As far as there were no functional disorders or complications in newborns with VMs and AVMs, treatment was not carried out in the neonatal period.

Cutaneous vascular lesions were seen in 53 (81.5%) IHs patients during the first month of life, anyway, as were no signs of functional disorders the therapy was not assigned before 4 weeks old. Among 14 children with numerous skin lesions multifocal hepatic hemangiomas were diagnosed in 8 (57.1%). Liver function was monitored, and regular sonography was performed to identify the hemangioma's activity level and its size. No correlation (p=0.2) was found between the number of skin lesions and the severity of liver lesions (Fig. 2). Congestive cardiac failure suddenly occurs in one patient in the third week of life. The treatment of hemangioma was performed only with corticosteroids, beta-blocker therapy could not be started because the child required inotropic support.

Diffuse hepatic hemangiomas were diagnosed in 3 newborns. Two of them were manifested right after the birth with clinical signs of liver failure (elevated transaminases levels, hepatocellular jaundice, hepatomegaly, coagulopathy), hypothyreosis, and congestive cardiac failure. Sonography was used as a screening method for hepatic IH diagnosis. For additional visualization CT (n=1) and MRI (n=1) were performed, where total replacement of normal liver tissue by vascular neoplasms were seen (Fig. 3). Treatment of diffuse hepatic hemangiomas included corticosteroids, beta-blockers, replacement therapy for hypothyroidism, and urgent resuscitation.

9 newborns had clinical signs of CHs. There were CHs of lower extremities (n=2), liver (n=3), upper extremities (n=2), hairy part of the head (n=2). CHs of superficial tissues were diagnosed on examination by typical diagnostic signs. Blood flow characteristics were determined by means of sonography; 2 patients required MRI for diagnosis. In 4 cases (44.4%) CHs were diagnosed prenatally, others – after birth (n=5; 55.6%). Congenital liver hemangiomas were diagnosed prenatally as accidental findings in two cases and in early neonatal period in one case. To assess the blood flow and tumor size sonography was performed in dynamics, for clear diagnosis MRI was performed. All CHs had a tendency to spontaneous involution within the first month of life without reference to their location. Treatment was not carried out to newborns with focal hemangiomas as there were no functional liver disorders and the tumor involution was observed at ultrasound control examination.

KHEs were diagnosed in 7 newborns: tumors' locations were upper extremity (n=1), shoulder and pectoral girdle (n=3), neck and mediastinum (n=1), neck, retroperitoneum and diaphragm (n=1), liver (n=1). The first clinical symptoms of the disease in 5 patients were visible since birth, in one case debut of the disease was at the age of 22 days. Tumor was visualized prenatally in 2 cases on routine ultrasound. KHE complications were thrombocytopenia (with platelet count of $8\text{-}10\times10^9$/l) in all 7 newborns (100%), pain syndrome, restriction of limb movement (n=2), upper airway compression which required prolonged (2 weeks) intubation, (n=1), hemothorax (n=1) in a child with neck, retroperitoneum and diaphragm KHE, and congestive cardiac failure in patient with liver KHE. Repetitive platelet concentrates transfusions had temporary and short-term effect. Short courses of corticosteroids were more effective for thrombocytopenia correction. Surgical treatment was not possible for the reason of the infiltrative tumor's growth and large volume of different tissue involved. Patients underwent prolonged courses of betablockers and vincristine outside the newborn period.

It was established that the complications of vascular anomalies in newborn period correlates with the localization of lesions (Pearson's criterion 0.71, $p<0.05$), with the size of mass (Pearson's criterion 0.53, $p<0.05$), and with type of vascular malformation or tumor (Pearson's criterion is 0.64, $p<0.05$).

DISCUSSION

Congenital vascular malformations have diverse clinical manifestations, sometimes only as a vascular spot, in other cases with symptomatic growing with critical disfigurements and mass, that may cause life-threatening conditions [8]. Among 238 children with vascular anomalies that were included to our study clinical presentation at the age of 0-28 days was seen in 170 (60.5%), whereas only 14 (8.2%) newborns required treatment. The indications for the treatment were clinically reasoned by development of dangerous complications, such as upper airways compression with respiratory failure when malformations were located within neck or head tissues; liver failure, hypothyreosis, cardiovascular failure in children with liver affection and thrombocytopenia in patients with aggressive vascular tumor – kaposiform hemangioendothelioma.

It is not only crucial to choose the optimal treatment method for vascular anomalies, but also to find an appropriate age for initiation of treatment. It is important to realize that not all vascular anomalies respond the treatment [9]. Moreover, they don't require treatment in all cases. Only the fact the child is diagnosed a vascular anomaly cannot become an indication for urgent surgical resection. Expectant management is a rational option in most cases, rather than impulsive treatment without comprehending the etiology and pathogenesis of the disease [10]. Some treatment methods that are used for vascular anomalies are aggressive, e.g. embolization may result into tissue ischemia; agents for sclerotherapy injected into vessels might cause tissues disruption, inflammation and encourage clotting. When large area is affected it may result into severe operational trauma. Most of LMs are isolated and don't threaten the life of a child. That is why

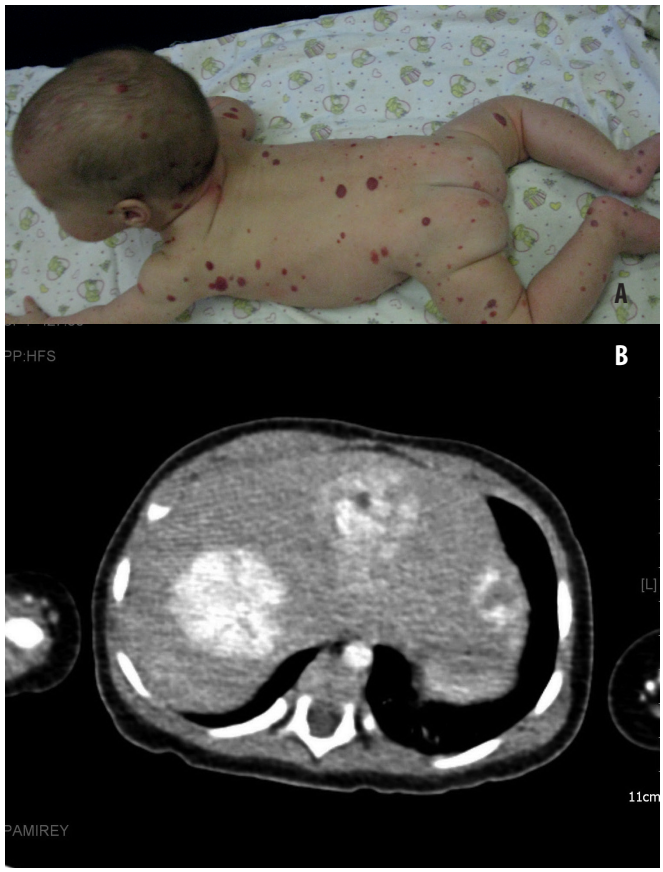

Fig. 2. Representative example of multiple infantile hemangioma. A - Photo, multiple cutaneous lesions. B - axial CT, several hepatic lesions with intervening normal hepatic parenchyma.

it is reasonable to avoid surgical resections or sclerotherapy in children of young age as LMs are typically located near vital organs and anatomical structures and therefore surgical interventions can result into vital functions compromise. [11]. According to the literature data, in about 50% cases, LMs are visible at birth. These data correlate with the results of our study: 53.8% cases of head and neck LMs were diagnosed in newborns, 6.4% of them required intubation and/or tracheostomy. Once a tracheotomy has been performed, it is common to wait until the airway is large enough to compensate for the initial cause of the obstruction This process may take many ears and it is common for children to need tracheostomy tube until the teenage years and sometimes ever longer [9]. For this reason, we performed partial resection and additional sclerotherapy in newborns in order to make decannulation procedure possible in early period. Recently, the frequent use of prenatal ultrasound has increased the likelihood of in utero diagnosis and, also, the use of ex utero intrapartum treatment procedures to secure the airway at birth in cases with upper airway obstruction [12].

VMs, that are sometimes called "cavernous hemangiomas" or "cavernomas", can present their first signs in early age, though the peak of clinical presentation appears by the age of 20 years. Less than 10% of extremities VMs are clearly seen before adolescence. According to this data in most cases there is no need in urgent therapy for newborns [13].

AVMs can manifest in newborns by a pink or red spot. They can in no way be distinguished from capillary spots. Rapid growth either complications development are not common for AVMs in young children therefore there is no need in urgent treatment [14].

Along first two months of life almost all IHs double their size. In a period of rapid growth, it can be seen how local IH covering 4 sm^2 turns into segmental IH covering 40 sm^2 [15]. IHs complications are related to their rapid growth in proliferation phase. Hepatic hemangiomas (infantile and congenital) are benign vascular tumors. The clinical behavior can be innocuous or life-threatening [16]. There is a mortality of 16% among children with multifocal and diffuse hepatic infantile hemangioma. Most of them had diffuse form, abdominal compartment syndrome, and heart failure. Being a potentially lethal conditions they require active treatment tactics in early age [17]. IH is high flow vascular tumors and can cause cardiac failure,

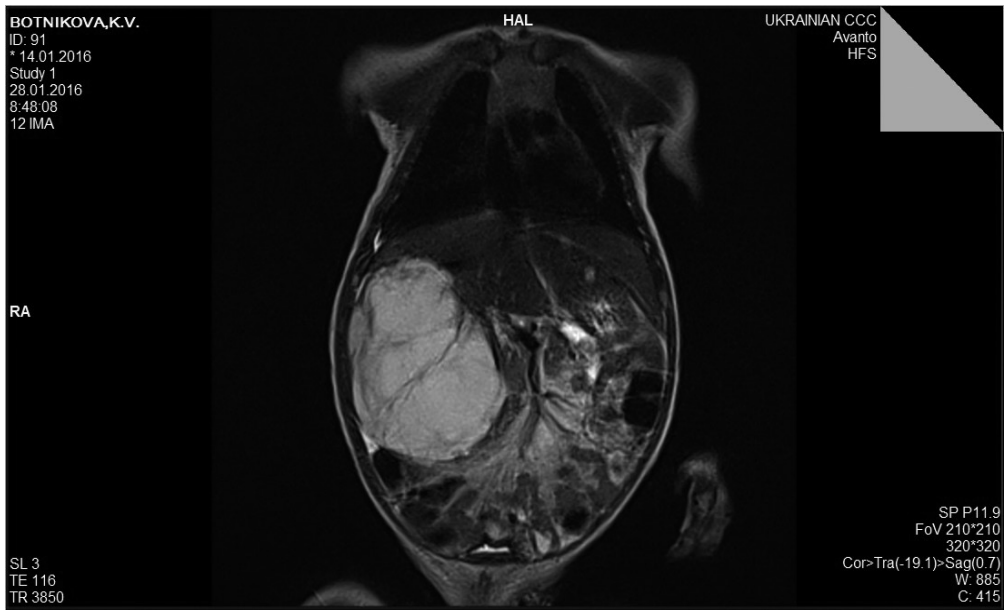

Fig. 3. Diffuse hepatic hemangioma. Coronal postcontrast MRI showing extensive vascular lesion replaces the hepatic parenchyma with little liver apparent.

it will develop during the proliferation period as shunting increases. Acquired consumptive hypothyroidism is specific for hepatic infantile hemangioma via high expression of type 3 iodothyronine deiodinase that inactivates the thyroid hormone [16]. Consumptive hypothyroidism does not occur in congenital hemangioma (hepatic or any other location).

CHs are rare tumors; their true incidence is unknown as only isolated cases are described in the literature. Moreover, not all authors identify such nosological unit [18]. 9 patients with CHs were included into our study, which amounts 3.2% of all clinical cases. CHs appear at the twelfth week of gestation therefore are usually diagnosed by fetal sonography. They reach their maximum size within terminal weeks of pregnancy. After, involution of CHs is observed during baby's first month of life. Consequently, dynamic observation is required.

The most dangerous complications of KHE relate to coagulation disorders stemming from thrombocytopenia, which is known as Kasbah-Merritt syndrome (phenomenon) [19]. When tumor resection is possible the hematological disorders are resolved the same day. Though in most cases radical tumor excision is not possible for surrounding tissues infiltration and tumor size. Heparin is contraindicated that was proved by experimental studies. Platelet concentrate hasn't got therapeutic effect in newborns with hemangioendotheliomas as can provoke fast tumor growth, considerable platelets disruption, which half-life period after transfusion ranges from 1 to 24 hours. Drug treatment should be started as soon as possible. That will allow decreasing tumor size and reducing hematological complications to a minimum. [20]. Nevertheless, by contrast with treatment tactics of IH, there are no international standards for borderline tumors treatment. Positive impact of steroids in newborns for thrombocytopenia correction was observed, though the extensive further treatment was nevertheless required.

CONCLUSIONS

It is challenging to receive a diagnosis of vascular anomaly in newborns as specific signs are absent and there are limitations for additional methods of examination. Clinical signs of vascular anomalies in neonatal period were seen in 57.5% children with vascular anomalies, and only 2.9% of them required treatment. Urgent treatment is advantageous only in cases when life-threatening complications develop, such as airways obstruction in newborns with head and neck LMs, cardiac and/or liver failure in patients with defuse and multifocal hepatic hemangiomas, and severe thrombocytopenia in children with kaposiform hemangioendothelioma.

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The work is carried out within the framework of the initiative research work of the Pediatric Surgery Department of Bogomolets National Medical University "Development and implementation of enhanced surgical management for young children with vascular malformations, that involves minimal invasive and combined treatment options with pathogenetic feasibility" (state registration No. 0113U004671).

ORCID and contributionship:
Iryna M. Benzar: 0000-0001-7637-7769 [A, D, F]
Anatolii F. Levytskyi: 0000-0002-4440-2090 [D, F]
Daria S. Diehtiarova: 0000-0002-2356-0874 [B, E, F]
Larysa Ya. Fedoniuk: 0000-0003-4910-6888 [C, E]
Yaroslav S. Stravskyy: 0000-0001-6541-9097 [C, F]
Daria A. Merkulova: 0000-0002-5021-2349 [E, F]
Petro A. Sas: 0000-0003-1649-4087 [C]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna M. Benzar
Bogomolets National Medical University
10G Vitryani Gory str, apt. 32, 04132 Kyiv, Ukraine
tel: +0380951295882
e-mail: ira_benzar@yahoo.com

Received: 22.04.2020
Accepted: 07.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

THE DYNAMICS OF NEUROHUMORAL MEDIATORS OF VASOCONSTRICTION AND VASODILATION AND TROPONIN I IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION DEPENDING ON THE DEGREE OF CONCOMITANT OBESITY

DOI: 10.36740/WLek202009208

Nataliya G. Ryndina, Pavlo G. Kravchun, Olexandra S. Yermak, Kateryna M. Borovyk, Ganna Yu. Tytova, Mykhailo I. Kozhyn
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: is to evaluate copetin's, MRproADM's and troponin's I dynamic in patients with acute myocardial infarction depending on the degree of concomitant obesity.

Material and methods: The study included 105 patients with AMI. There were formed 2 groups: 1st group of patients with AMI and concomitant obesity (n=75), 2nd group – patients with AMI without obesity (n=30). 37 patients had obesity of the I degree, 38 patients - II degree. The groups were comparable in age and gender. Copeptin, MRproADM, troponin I were determined by enzyme immunoassay method. Data are presented as mean values and the error of the mean (M±m). Differences were considered statistically significant at $p<0,05$.

Results: It was found an increased copeptin's level by 73,8 % ($p<0,001$) in obesity I degree and by 205,9 % in obesity II degree compared with group with isolated AMI, MRproADM - by 30,68 % ($p<0,001$) and 54,5 % ($p<0,001$) respectively. Concentration of copeptin was higher by 76 % ($p<0,001$) in patients with AMI and II degree obesity comparing to patients with obesity of I degree, and MRproADM - by 18,3% ($p<0,001$) respectively. Troponin I value fully corresponded the comparison group both in obesity of I degree and II degree ($p>0,05$).

Conclusions: The present study provides evidence that a high activity of copeptin and MRproADM in patients with AMI and obesity of I degree with an excessive activity of a marker of vasoconstriction copeptin in conditions of moderate inadequate to the needs MRproADM functioning in patients with obesity of II degree.

KEY WORDS: acute myocardial infarction, obesity, vasoconstrictors, vasodilators, copeptin, MRproadrenomedulin

Wiad Lek. 2020;73(9 p. II):1940-1943

INTRODUCTION

Cardiovascular diseases (CVD) occupies the first place in the structure of morbidity, disability and mortality worldwide. Priority in the structure of the cardiovascular disease belongs to coronary artery disease (CAD) and especially to its acute form - acute myocardial infarction (AMI). The destabilization of CAD in the form of the development of AMI remains an important cause of disability and mortality worldwide [1-3]. Every year in the world there are more than 15 millions of new cases of AMI. By 2030, it is projected that about 23.6 million people will die due to heart attacks and mainly from heart disease and stroke. The leading nosological form in the structure of CAD is the AMI with elevation of ST segment (STEMI) for many years [4-5].

According to World Health Organization (WHO), obesity is recognized as a non-infectious «epidemic of the 21st century» and is one of the five major risk factors of death. In addition, obesity is a risk factor for the development of CVD, progression and destabilization of CAD [6, 7]. As a result of the INTERHEART study, it has been proved that obesity is an independent risk factor for CAD [8]. Obesity is not only an independent factor in the risk of cardiovascular complications, but also is a trigger mechanism for the development of CVD [9]. Despite the existence of a close relationship between obesity and cardiovascular disorders, the molecular genetic bases remain not fully defined. It is known that adipose tissue secretes a large number of biologically active substances - adipocytokines, which can provide either local auto- and paracrine effects or systemic endocrine and pro-inflammatory effects, as well as to promote and counteract the development of cardiovascular disease [10, 11, 12]. Additionally, adequate therapy for hyperglycemia leads not only to lowering insulinemia, but also to a decreasing in the content of sCD40-ligand, which contributes to inhibition of immune-inflammation and thrombosis [13-16].

In accordance with European and Ukrainian guidelines increased concentration of troponin I is a diagnostic criteria for ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (nonSTEMI) [17, 18]. But searching for new, more specific, prognostically valuable markers today takes the attention of the world medical community. Activation of neurohumoral systems plays an important role in the pathogenesis of AMI under conditions of comorbid obesity [19]. Most

Table 1. The levels of copetin, MRproADM and troponin I in patients with acute myocardial infarction depending on the degree of concomitant obesity (M±m)

Indicator, units	Patients with AMI and obesity		Patients with AMI and obesity
	Obesity of I degree	Obesity of I degree	
	1	2	3
Copeptin, ng/ml	145,86±3,76	256,73±11,37	83,9±5,38 $p_{1 \text{ and } 2}$<0,001 $p_{1 \text{ and } 3}$<0,001 $p_{2 \text{ and } 3}$<0,001
MRproADM, ng/ml	586,4±12,12	694,06±19.99	449,03±6,49 $p_{1 \text{ and } 2}$<0,001 $p_{1 \text{ and } 3}$<0,001 $p_{2 \text{ and } 3}$<0,001
Troponin I, ng/ml	6,53±1,48	6,44±1,37	6,98±1,91 $p_{1 \text{ and } 2}$>0,05 $p_{1 \text{ and } 3}$>0,05 $p_{2 \text{ and } 3}$>0,05

neurohumoral shifts are mediated by vasoconstrictor and vasodilator responses. Given this fact, it is interesting to study the C-terminal part of the prohormone vasopressin (vasoconstriction mediator) - copeptin and midregional proadrenomedullin (MRproADM) (vasodilator mediator).

THE AIM

The aim of the present research is to evaluate copetin's, MRproADM's and troponin's I dynamic in patients with acute myocardial infarction depending on the degree of concomitant obesity.

MATERIALS AND METHODS

SUBJECT RECRUITMENT

Between 2013 and 2015, eligible people were identified and recruited from the electoral roll, and invited to attend a screening clinic close to their home. On arrival at the clinic, the trial was explained to each participant and written consent was obtained. A risk factor questionnaire covering aspects of medical history and lifestyle relevant to CVD was completed. Height, weight, girth at hips and waist, and blood pressure were measured. The study included 105 patients with AMI and obesity, who were treated at the intensive care unit and cardiological department at the hospital No 27. We formed 2 groups: 1st group of patients with AMI with concomitant obesity (n=75), 2nd group – patients with AMI and without obesity (n = 30). 37 patients had obesity of the I degree, the 38 patients - II degree according to the body mass index (BMI). The average age of patients in group 1 was 65,96±1,11 years, and 2 groups - 63,46±1,76 years (p>0,05). The groups were comparable in gender. The exclusion criteria were acute and chronic inflammatory processes, diffuse connective tissue diseases, oncological diseases, concomitant diseases of the thyroid gland, and the presence of symptomatic hypertension. Diagnosis of AMI verified according to ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [9]. The presence of obesity was established according to the classification of WHO, 1997 [19] under the BMI >30 kg/m^2 according to the formula: BMI (kg/m^2) = body weight/(height)^2.

IMMUNOASSAY METHOD

Copeptin was determined using the Human Copeptin (Copeptin) ELISA Kit (Shanghai, China). MRproADM was determined using «Human mid-regional pro-adrenomedullin (MRproADM)» (Biological Technology, Shanghai). Troponin I was determined using «Troponin I» with an enzyme immunoassay method in the blood serum (Ham, Russian Federation).

STATISTICAL METHODS

Data are presented as mean values and the error of the mean (M±m). Statistical analysis of the difference between dispersions in the groups was evaluated using F-Fisher's criterion. An assessment of the differences between groups in a distribution close to normal was carried out using the Student's criteria. Differences were considered statistically significant at p<0,05.

RESULTS

Copeptin and MRproADM showed significant differences in patients with AMI and obesity of I and II degree, comparing with group represented by AMI patients without obesity. It was found an increased copeptin's level by 73,8 % (p<0,001) in obesity I degree and by 205,9 % in obesity II degree compared with the comparison group, MRproADM - by 30,68 % (p<0,001) and 54,5 % (p<0,001), respectively (Table I).

Concentration of copeptin was higher by 76 % (p<0,001) in patients with AMI and II degree obesity comparing to patients with AMI and obesity of I degree, and MRproADM - by 18,3% (p<0,001) respectively. As for the content of troponin I, its value fully corresponded the comparison

group both in obesity of I degree and II degree (p>0,05). Comparison of the concentrations of this parameter in obesity of I degree and II degree in patients with AMI did not reveal any significant differences (p>0,05). The ranking of indicators according to the degree of their differences in obesity of 1st degree from the comparison group using the F-criterion determined that the cluster of pronounced disorders included both parameters - copeptin (F=77,9; p<0,001) and MRproADM (F=82,5; p<0,001). Thus, in patients with AMI and obesity of I degree, it was found high activity of both markers (copeptin and MRproADM) - that is confirmed by approximately the equivalent degree of deviation (F=77,9 and F=82,5 respectively). The obtained data prove opinion about work of system of vasoconstrictors and vasodilators in the form of adaptive stress due to the adequate compensatory mechanisms presented by MRproADM. According to the obtained results while comparison of indicators deviation by the degree of their differences in obesity of the II degree (according to the F-criterion), it can be distinguished that a cluster of very expressive changes (F=100) included increased level of copeptin (F=177,9; p<0,001). The significant growth was noted for MRproADM (F=99,5; p<0,001). In order to evaluate the changes in copeptin and MRproADM with varying degrees of overweight in patients with AMI, a ranking was conducted for the degree of their deviation in obesity of II degree from the group of patients with obesity of I degree. According to the obtained results, it can be distinguished a cluster of very expressive changes (F=100) and moderate changes (50>F>10). Very significant deviations were found for copectin (F=107,9; p<0,001), where as it was detected moderate deviations (F=21,2; p<0,001) for MRproADM.

DISCUSSION

The obtained results of indicators deviation comparison by the degree of their differences in obesity of the II degree indicate that the presence of II degree obesity in patients with AMI is accompanied by a disproportionate increase in the concentrations of vasoconstrictors and vasodilators with a lower activity of last one, which are represented by MRproADM, while the vasoconstrictive activity (due to copeptin) occupies the first rank position. The obtained results of evaluation the changes in copeptin and MRproADM with varying degrees of overweight in patients with AMI indicate that the appearance of AMI in patients with concomitant obesity of II degree comparing with obesity of I degree was excessive activity of copeptin, which are the stress marker, indicator of platelet aggregation and vasoconstriction in conditions of moderate increase of MRproADM, which indicates an inadequate vasodilator system functioning. Thus, the imbalance in the work of vasoconstrictors and vasodilators in patients with AMI clearly manifests itself at the obesity of the II degree. The findings are in line with the findings of the specialists of the world medical community. Thus, according to Morgentaler N., the activity of copeptin increases in patients with cardiovascular events, including AMI and heart failure [20]. Similar results were obtained in the LAMP study [21]. On the other hand, body mass growth is accompanied by an increase in the activity of copeptin, which some authors consider as a predictor of obesity [22]. However, there is evidence that copeptin has a strong association with insulin resistance and, as a result, displays indicative properties in patients with obesity [23, 24, 25]. This fact explains the results obtained in our study on the maximum activity of copeptin in a cohort of patients with AMI and obesity of II degree, since the progression of the severity of obesity is associated with a proportional increase in the incidence of insulin resistance [24].

CONCLUSIONS

In conclusion, the present study provides evidence that a high activity of mediator of vasoconstriction copeptin and mediator of vasodilation MRproADM in patients with acute myocardial infarction and concomitant obesity of I degree. The feature of the development of acute myocardial infarction in patients with obesity of II degree compared with obesity of I degree is an excessive activity of a marker of vasoconstriction - copeptin in conditions of moderate inadequate relative to the needs of the functioning of MRproADM.

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The work is performed within research of Department of Internal Medicine №2, Clinical Immunology and Allergology named after L.T. Malaya of the Kharkiv National Medical University «Coronary artery disease in the conditions of a polymorbydity: pathogenetic aspects of development, current, diagnostics and improvement of the treatment» (№0118U000929), the term of performance is 2017-2019.

ORCID and contributionship:
Nataliya G. Ryndina: 0000-0002-1815-1965 [D]
Pavlo G. Kravchun: 0000-0002-8285-6763 [F]
Olexandra S. Yermak: 0000-0002-59571567 [C]
Kateryna M. Borovyk: 0000-0003-2155-4865 [B]
Ganna Yu. Tytova: 0000-0001-6876083X [A]
Mykhailo I. Kozhyn: 0000-0002-8359-8890 [E]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Nataliya G. Ryndina
Kharkiv National Medical University
4 Nauky st., 61022 Kharkiv, Ukraine
tel:+380501635337
e-mail: nryndina81@gmail.com

Received: 11.10.2019
Accepted: 09.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

EFFICACY OF SPECIFIC PREVENTION OF INFLUENZA IN INDIVIDUALS WITH POLYMORPHISMS ARG753GLN OF TLR-2, LEU412PHE OF TLR-3, ASP299GLY OF TLR-4 GENES

DOI: 10.36740/WLek202009209

Nataliia O. Pryimenko, Tetiana M. Kotelevska, Tetiana I. Koval, Vadym A. Bodnar, Liudmyla M. Syzova, Stanislav S. Rudenko
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

The aim: is to study the efficacy of influenza vaccination for individuals with polymorphism Arg753Gln of TLR-2 gene, Leu412Phe of TLR-3 gene, and Asp299Gly of TLR-4 gene.

Materials and methods: 66 people with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, TLR-4 genes, aged 18-63, were inoculated with anti-influenza vaccine. The genotyping of Arg753Gln polymorphic site of TLR-2, Asp299Gly of TLR-4, and Leu412Phe of TLR-3 gene was carried out by polymerase chain reaction with oligonucleotide primers usage. The immunological efficacy of vaccination was evaluated by seroconversion, seroprotection, and dynamics of mean geometric titers of antibodies.

Results: It has been established that individuals with mutant genotypes Arg/Gln of TLR-2, Leu/Phe, Phe/Phe of TLR-3, Asp/Gly of TLR-4 genes have a vaccinal response to administering anti-influenza vaccine at the level of subjects with normal distribution of TLR alleles, as evidenced by the growth in dynamics of mean geometric titers of antibodies to vaccine strains, the level of seroprotection and seroconversion. Clinical and epidemiological efficacy of vaccination in this category of people is characterized by: reduction of ARI cases in the postvaccinal period by 2,0-3,0 times; prevention of pneumonia in all vaccinated subjects; decrease in the frequency of bronchitis by 2,5-3,8 times.

Conclusions: Effectiveness of influenza vaccination in individuals with Arg573Gln polymorphism of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes by immune and clinical epidemiological parameters is determined at the level of vaccinated subjects with normal distribution of TLR-2, TLR-3, TLR-4 alleles. Specific influenza immunization of people with polymorphic modified genotypes of TLR-2, TLR-3, TLR-4 genes can prevent the development of pneumonia and reduce the incidence of bronchitis.

KEY WORDS: vaccination, genotype, influenza, polymorphism, TLR

Wiad Lek. 2020;73(9 p. II):1944-1949

INTRODUCTION

Influenza and influenza-like diseases remain one of the most urgent medical and social problems due to the high specific occurrences of infectious pathology (80-90%), as well as the risk of severe complications and exacerbations of chronic diseases [1]. According to the assessment of WHO influenza afflicts up to 500 million people, 2 million of them die each year. The largest number of fatal influenza cases is due to complications that predominantly affect the patients at risk (pregnant women, people with diabetes, obesity, chronic diseases of the lungs and heart, and persons of advanced age groups) [2, 3].

According to the WHO experts, effective control of influenza is possible only through mass immunization. The intensity and nature of the immune response in vaccination depends on the functional state of the immune system [4]. Nowadays, it is known that selective substitutions in genomic DNA (single-nucleotide polymorphism) lead to changes in the structure of TLR, thus disrupting the recognition of pathogen-associated molecular structures, functioning of innate immunity and, consequently, changing the immune response to infectious agents and vaccination [5].

In recent years, it has been found that recognition of structural proteins of influenza virus involves TLR-2 and TLR-4, and of viral RNA – TLR-3 [6-9]. Association of polymorphisms Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 gene with the development of severe influenza and influenza-associated pneumonia in patients without generally accepted risk factors has been detected [10-12]. However, the efficacy of specific prevention of influenza in individuals with Arg753Gln polymorphism of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes has not been investigated and has become the subject of our study.

THE AIM

The aim of the research is to study the efficacy of vaccination against influenza among people with polymorphism Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes.

MATERIALS AND METHODS

To study the effectiveness of influenza vaccination among people with polymorphism Arg753Gln of TLR-2, Le-

u412Phe of TLR-3, Asp299Gly of TLR-4 genes, 66 people aged 18-63 (mean age – 31.2 ± 1.48) were inoculated with anti-influenza vaccine, women – 48 (72.7%) men – 18 (27.3%). The vaccinated subjects did not have generally recognized risk factors for the development of complications of influenza (pregnancy, obesity, diabetes, immunosuppressive disorders and chronic diseases of the lungs, heart, kidneys, liver, etc.). As a result of their molecular genetic examination, the following genotypes of the studied TLRs were obtained: TLR-2 – Gln753Gln, Arg753Gln; TLR-3 – Leu412Leu, Leu412Phe, Phe412Phe; TLR-4 – Asp299Asp, Asp299Gly. The vaccinated patients with polymorphic modified TLR genotypes were divided into as follows: Leu/Phe of TLR-3 – 23, Phe/Phe of TLR-3, Asp/Gly of TLR-4 and combination of mutant genotypes of TLR-2, TLR-3, TLR-4 – 6 each, Arg/Gln of TLR-2 – 5 people. The obtained results were compared with those of 20 healthy individuals with normal alleles distribution of TLR-2, TLR-3, TLR-4 genes, equivalent in terms of gender and age.

All studies were performed after signing the informed consent. The work was approved by the Commission on Ethical Issues and Bioethics of the Ukrainian Medical Stomatological Academy.

Immunization was performed by standard method with vaccine Influvac® (Solvay Pharmaceuticals, the Netherlands) containing relevant strains for epidemic seasons of 2011/2012, 2012/2013, 2013/2014. All examined patient were vaccinated against influenza for the first time. Vaccination was carried out after the doctor's examination.

The immune response to vaccination was evaluated in the reaction of hemagglutination inhibition (RHGI) based on the study of paired blood sera, collected prior to immunization and 28 days after the administration of the vaccine. The composition of RHGI was carried out according to the standard methodology with the use of diagnostic preparations «Dry influenzal diagnosticum for the reaction of hemagglutination inhibition» (Russia). The immunological efficiency of vaccination was estimated by seroconversion (the number of increments of specific antibody titers was 4 times or more), seroprotection (percentage of subjects with titers 1:40 and higher after vaccination) and the dynamics of the level of the mean geometric titers of antibodies. The analysis took into account the initial level of anti-influenza antibodies.

Assessment of epidemiological and clinical effect of vaccination was performed by comparing the number of episodes of acute respiratory infections (ARI), the severity of their progress and development of complications arising in the epidemic season. The period of 6 months after vaccination was analyzed, as well as the same period of the year before immunization.

Polymorphic region Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes were genotyped by polymerase chain reaction using oligonucleotide primers. The amplification was performed using «Tertsyk» amplifier («DNA-technology», Russia).

Mathematical processing of data was carried out by using the software «STATISTICA for Windows 7.0» (StatSoft Inc., USA) and MS Excel. The probability of differences in the results of the studied groups was determined using the Student's t-criterion. When comparing the frequencies of binary traits in two related groups, McNamara's criterion was used; in other cases, Fischer's exact criterion was applied. For all types of analysis, the differences were considered statistically significant at $p<0.05$.

RESULTS

The study has shown that the condition of immunity before vaccination among all participants was characterized by a high level of seroprotection with the highest level of protection in individuals with mutant homozygous genotype Phe/Phe of TLR-3, heterozygous Asp/Gly of TLR-4 and combination of mutations in TLR-2, TLR-3, TLR-4 genes – 83.3%-100.0% for all vaccine strains. Seronegative to vaccination were individuals with normal distribution of alleles of the studied TLRs (A/H1N1 and A/H3N2 – 10.0% each, B – 5.0%) and heterozygous genotype Leu/Phe of TLR-3 (A/H1N1 – 17.4%, B – 4.3%).

While studying immunological efficacy of vaccination, it was found that 28 days after immunization, there was an increase in the percentage of individuals with protective antibody titer in all vaccinated individuals regardless the initial level of influenza antibodies. Thus, after vaccination, the percentage of individuals with protective antibody titers among those who had the pre-vaccinal level of ≤ 1:20 was: with normal distribution of TLR alleles to serotype A/H1N1 – 80.0%, A/H3N2 – 50.0%, with genotype Leu/Phe of TLR-3 to A/H1N1 – 100.0%, A/H3N2 – 75.0%, B – 33.3%. It should be noted that among the examined individuals with mutant genotypes Phe/Phe of TLR-3, Asp/Gly of TLR-4, Arg/Gln of TLR-2 and mutation combinations in TLR-2, TLR-3, and TLR-4 genes, individuals with the initial titer of ≤ 1:20 were determined only for individual strains of influenza, with a total of 100% protective levels of specific antibodies after vaccination. By the level of seroprotection, individuals with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, TLR-4 with a low initial antibody titer (≤ 1:20) did not differ significantly.

While studying the level of seroprotection among the examined groups in general (regardless of the initial level of influenza antibodies) before and 28 days after vaccination, the percentage of persons with protective titer in all influenza strains was determined among vaccinated individuals with both mutant genotype and normal distribution of alleles of TLR-2, TLR-3, TLR-4. At the same time, the level of seroprotection was significantly higher to A/H1N1 serotype in subjects with normal distribution of alleles of TLR (95.0 ± 4.9, before vaccination – 75.0 ± 9.7, $p<0.05$) and genotype Leu/Phe of TLR-3 (100.0 ± 2.1, before vaccination – 69.6 ± 9.6, $p<0.005$) and A/H1N1 – with genotype Arg/Gln of TLR-2 (100.0 ± 4.5, before vaccination – 60.0 ± 21.9, $p<0.05$).

The analysis of the seroconversion level showed that the vaccine response among the individuals with polymorphic modified genotypes of TLR-2, TLR-3, and TLR-4 did not depend on the initial level of specific antibodies and was

Tab. 1. Seroconversion level in individuals with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, TLR-4 with antibody titer before vaccination ≤ 1:20 and ≥ 1:40, abs. number (%)

TLR genotypes	Serotypes of influenza virus	Number of people with titer ≤ 1:20 before vaccination		Number people with seroconversion		Number of people with titer ≥ 1:40 before vaccination		Number people with seroconversion	
		abs	%	abs	%	abs	%	abs	%
Normal distribution of TLR alleles (n = 20)	A/H1N1	5	25.0	2	40.0	15	75.0	3	20.0
	A/H3N2	4	20.0	2	50.0	16	80.0	3	18.7
	B	2	10.0	0	0.0	18	90.0	7	38.9
Leu/Phe of TLR-3 (n = 23)	A/H1N1	7	30.4	7	100.0*	16	69.6	8	50.0
	A/H3N2	4	17.4	1	25.0	19	82.6	7	36.8
	B	6	26.1	0	0.0	17	73.9	3	17.6
Phe/Phe of TLR-3 (n = 6)	A/H1N1	0	0.0	0	0.0	6	100.0	4	66.7
	A/H3N2	0	0.0	0	0.0	6	100.0	2	33.3
	B	1	16.7	1	100.0	5	83.3	0	0.0
Asp/Gly of TLR-4 (n = 6)	A/H1N1	1	16.7	1	100.0	5	83.3	1	20.0
	A/H3N2	1	16.7	1	100.0	5	83.3	1	20.0
	B	1	16.7	1	100.0	5	83.3	0	0.0
Arg/Gln of TLR-2 (n = 5)	A/H1N1	2	40.0	2	100.0	3	60.0	2	66.7
	A/H3N2	0	0.0	0	0.0	5	100.0	2	40.0
	B	1	20.0	1	100.0	4	80.0	2	50.0
Combinations of mutant TLR genotypes (n = 6)	A/H1N1	1	16.7	1	100.0	5	83.3	2	40.0
	A/H3N2	0	0.0	0	0.0	6	100.0	0	0.0
	B	0	0.0	0	0.0	6	100.0	1	16.7

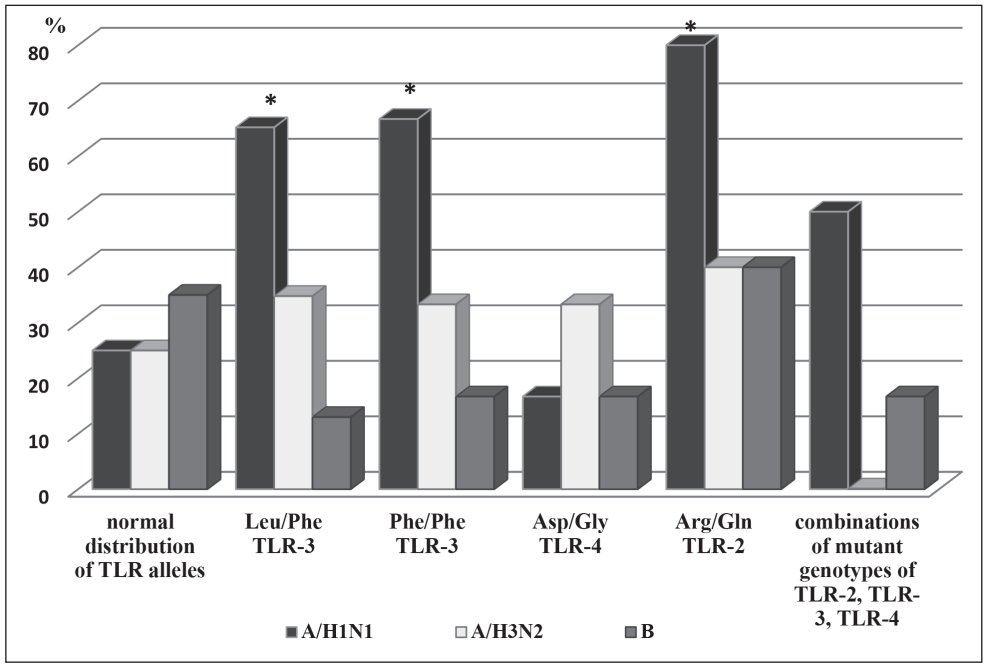
Note: * – $p<0.05$, as compared to indicators of individuals with normal distribution of alleles of TLR-2, TLR-3, TLR-4.

determined at the level of vaccinated subjects with normal distribution of TLR alleles. Thus, by the level of seroconversion, the vaccinated subjects with mutant genotypes of TLR-2, TLR-3, TLR-4 and normal distribution of TLR alleles with the initial titer of specific antibodies ≤ 1:20 did not differ significantly. The exception were the individuals with the Leu/Phe genotype of TLR-3, in which the 4-fold increase in the antibody to the A/H1N1 serotype was 100.0% as against 40.0% ($p=0.04$) in the vaccinated subjects with normal distribution of TLR alleles. In vaccinated individuals with mutant genotypes Phe/Phe of TLR-3, Asp/Gly of TLR-4, Arg/Gln of TLR-2 and their combination that had the initial titer of ≤ 1:20 to individual strains of influenza, 100% seroconversion was obtained (Table I).

As shown in Table I, among the individuals with the initial titer of anti-influenza antibodies ≥1:40, there was no significant difference in vaccine response between the mutant genotypes of examined TLR and normal distribution of alleles. By the level of seroconversion, individuals with polymorphic modified genotypes of TLR-2 and TLR-3 were distinguished by the vaccinal response to A/H1N1 serotype from vaccinated individuals with normal distribution of alleles of TLR-2, TLR-3, and TLR-4 (Fig. 1).

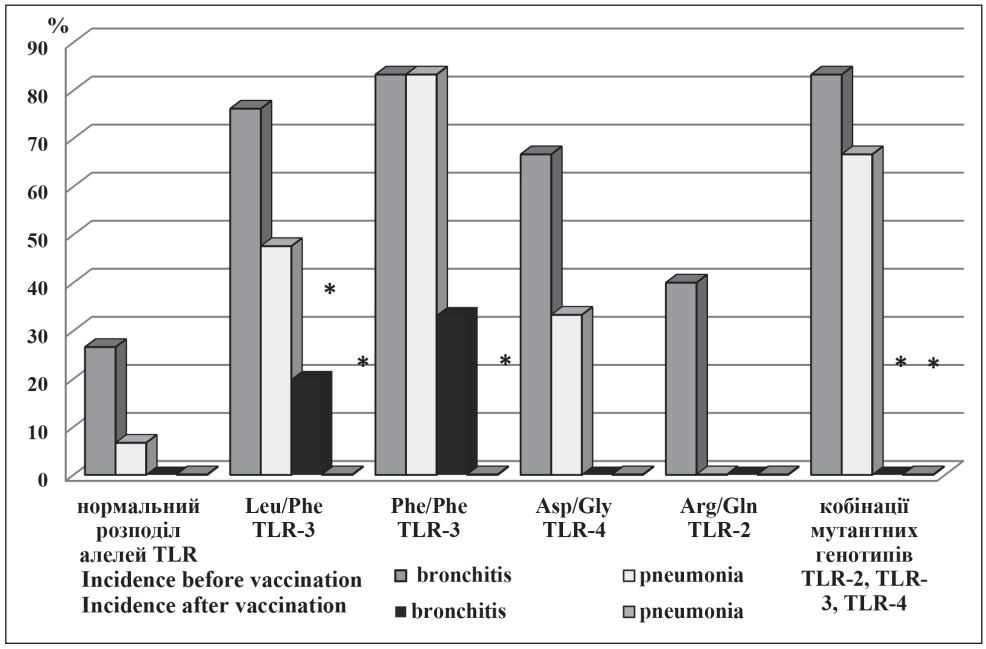
Hence, the number of 4-fold seroconversions was significantly higher in individuals with genotype Leu/Phe of TLR-3 (65.2% ± 9.7, $p<0.05$), Arg/Gln of TLR-2 (80.0% ± 17.9, $p<0.05$) and with a reliability tendency to Phe/Phe of TLR-3 (66.7% ± 19.2, $p<0.05$) as compared to vaccinated subjects with normal distribution of TLR alleles (25.0% ± 9.7). Seroconversion level for serotypes A/H3N2 and B in individuals with polymorphic modified genotypes and normal distribution of TLR-2, TLR-3, and TLR-4 alleles were not significantly different.

The study of the dynamics in the mean geometric titers of antibodies showed that on the 28th day of vaccination process, the titers among all the individuals of the vaccinated groups increased. The comparative analysis of the mean geometric titers after vaccination among the individuals with mutant genotypes TLR-2, TLR-3, TLR-4 and normal distribution of TLR alleles showed that vaccinated persons with polymorphic modified TLR genotypes had significantly higher rates for individual vaccine strains. Thus, the average geometric titers to A/H1N1 strains were higher in individuals with genotype Leu/Phe of TLR-3 by 2,4 (126.9, $p<0.005$), Phe/Phe of TLR-3 by 4,2 (226.3, $p<0.001$), Arg/Gln of TLR-2 – by 3 (160.0, $p<0.02$), combinations of mutations in TLR-2, TLR-3, TLR-4 genes – by 3,3 times (179.6, $p<0.01$), as compared to vaccinated individuals with normal distribution of TLR alleles (54.0). The corresponding index was significantly higher to the A/H3N2 strain in vaccinated individuals with Arg/Gln genotype of TLR-2 (320.0 with normal distribution of TLR alleles – 100.8, $p<0.0005$).



Note: * – p<0.05 in comparison with the indicators of individuals with normal distribution of alleles of TLR-2, TLR-3, TLR-4 (the level of significance was obtained according to Student's criterion)

Fig. 1. Seroconversion level in individuals with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, TLR-4



Note: * – p<0.05 in comparison with pre-vaccination rates (McNemar's significance level)

Fig. 2. The frequency of complications of acute respiratory infections by the inflammatory processes of lower airways before and after vaccination in individuals with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, TLR-4 genes

Follow-up monitoring of the vaccinated subjects during 6 months indicated a pronounced prophylactic effect of vaccination in relation to subsequent ARIs in the examined individuals with polymorphic modified genotypes of TLR-2, TLR-3, TLR-4 and with normal distribution of TLR alleles. Thus, the percentage of persons with acute respiratory infections after vaccination decreased by 2,1 (from 91.3% to 43.5%, p<0.0005) among the subjects with Leu/Phe genotype of TLR-3, Phe/Phe of TLR-3 and combination of mutations in TLR-2, TLR-3, TLR-4 genes by 2 (from 100.0% to 50.0%, p=0.04), Asp/Gly of TLR-4 – by 3 (from 100.0% to 33.3%, p<0.01), Arg/Gln of TLR-2 and normal distribution of TLR alleles – by 2,5 times (from 100.0% to 40.0%, p=0.03 and from 75.0% to 30.0%, p=0.004, respectively). It should be noted that against the background of vaccination, there was a decrease in the frequency of episodes of acute respiratory infections in people with mutant genotypes of TLR-2, TLR-3, TLR-4 and with normal distribution of TLR alleles who were ill more than 4 times during the epidemic season prior to vaccination. In the majority of patients with 4 or more episodes of acute respiratory infections before vaccination there was a reduction in their frequency by 1-2 times after vaccination: with mutant genotypes Leu/Phe of TLR-3 – in 62.5% (p=0.02), Phe/Phe – in 75.0% (p<0.05) and combination of mutations of TLR-2, TLR-3, and TLR-4 genes in 50.0% (p<0.05) of subjects. In the rest of examined individuals, namely with genotype Leu/Phe of TLR-3 – 37.5%, Phe/Phe – 25.0%, with combination of mutant genotypes of TLR-2, TLR-3, TLR-4 and normal distribution of TLR

alleles (50.0% each) no case of ARI in the post-vaccination period was registered.

After vaccination, the course of ARI has also changed. Among individuals with mutant genotypes of TLR-2, TLR-4 and normal distribution of TLR alleles, ARIs had an exclusively (100.0%) mild course, whereas the percentage of lung and mild-to-severe forms was as follows: with Arg/Gln genotype of TLR-2: 20.0% and 80.0%, Asp/Gly of TLR-4 – 33.3% and 66.7%, with normal distribution of TLR alleles – 53.3% and 46.7% respectively. In general, there was a significant decrease in the percentage of medium-severe acute respiratory infections against the background of vaccination among individuals with genotype Leu/Phe of TLR-3 by 2,4 times (30.0%, before vaccination – 71.4%, p=0.02), Phe/Phe and combination of mutations in TLR-2, TLR-3, TLR-4 genes – by 3 times (33.3% each, before vaccination – 100.0% each, p=0.04).

It has been established that influenza vaccination is able to prevent the development of complications of acute respiratory infections both in individuals with mutant genotypes of TLR-2, TLR-3, TLR-4, and with the normal distribution of TLR alleles. Thus, after vaccination, the percentage of patients with complicated course of ARI decreased: with genotype Leu/Phe of TLR-3 by 2,0 (from 80.9% to 40.0%, p=0.02), Phe/Phe of TLR-3 and combination of mutations in TLR-2, TLR-3, and TLR-4 genes – by 3 times (from 100.0% to 33.3%, p=0.02). In the examined individuals with genotype Arg/Gln of TLR-2, Asp/Gly of TLR-4 and normal distribution of alleles of the studied TLRs, complications after vaccination were not registered at all (before vaccination in 40.0%, 66.7% and 33.3% respectively, p<0.05).

Vaccination against influenza proved to be an effective method for preventing the complications of acute respiratory infections by inflammatory processes of lower airways in all vaccinated groups (Fig. 2).

Thus, after vaccination, pneumonia was not registered in subjects with mutant genotypes and normal distribution of alleles of TLR-2, TLR-3, and TLR-4. At the same time, a significant reduction in the percentage of complications of ARI by pneumonia was noted in individuals with genotype Leu/Phe (0.0% before vaccination 47.6%, p=0.008) and Phe/Phe of TLR-3 (0.0% before vaccination 83.3%, p<0.01), as well as with combination of mutations in the examined TLR genes (0.0% before vaccination 66.7%, p<0.05).

Among the examined individuals with mutant genotypes of TLR-3, there was a decrease in the frequency of complications of ARI with bronchitis, namely: with Leu/Phe genotype – by 3,8 times (from 76.2% to 20.0%, p=0.003), Phe/Phe – by 2,5, but without reliable difference as compared with the index before vaccination (from 83.3% to 33.3% respectively). Among the patients with normal distribution of alleles of TLR, polymorphic modified genotypes of TLR-2, TLR-4 and their combinations with TLR-3, this complication after vaccination during epidemic season was not recorded, and immunization rate was as follows: with combinations of mutant genotypes of TLR-2, TLR-3, TLR-4 – 83.3% (p<0.01), Asp/Gly of TLR-4 – 66.7% Arg/Gln of TLR-2 – 40.0% with normal distribution of alleles of TLR – 26.7%.

DISCUSSION

Toll-like receptors (TLRs) and their intracellular signaling molecules play an important role in congenital immunity. In this study, we studied the relationship between polymorphism in the TLR gene and specific immune responses to the influenza vaccine. Previously, we found that the polymorphism of Arg573Gln TLR-2, Leu412Phe TLR-3, Asp299Gly TLR-4 genes among the individuals without generally accepted risk factors for influenza affects the course of the disease, the incidence of flu-associated pneumonia, its severity and development of acute respiratory distress syndrome and multiple organ failure [11, 12]. These findings allow us to suggest that differences in the genes involved in the antigen recognition process and in controlling the body's protective responses can also determine the different nature of specific immunological responses to vaccination. It is also known that among healthy young people there is a significant proportion of those who, after vaccination against influenza, do not produce protective titers of specific antibodies. Therefore, the important task is to identify these individuals before vaccination and an attempt to modify the type or dose of the vaccine to achieve a reduction in the number of unprotected individuals in the vaccinated [13, 14].

We have not identified association between the polymorphism of the Arg573Gln TLR-2 genes, Leu412Phe TLR-3, Asp299Gly TLR-4, and the impairment of the immune response to the administration of the influenza vaccine. Individuals with mutant genotypes TLR-2, TLR-3, and TLR-4 had a vaccine response at the level of the subjects with normal distribution of TLR alleles, as evidenced by the level of seroprotection, seroconversion, and dynamics of mean geometric antibody titers on day 28 of immunization. The results obtained can be explained by a survey of a small group of individuals selected for the study (n = 66). Historically, titres of specific antibodies are used to evaluate vaccine efficacy, but they do not reflect the full complexity of human immune responses to vaccination. Therefore, there is a need for additional studies in order to determine the connection between polymorphous modified Arg573Gln TLR-2, Leu412Phe TLR-3, Asp299Gly TLR-4 genes, with a change in the immune response to influenza vaccines in groups different from those selected for this study and to determine the cause / an effect relationship between these genes and the antibody response. The results will help establish the genetic basis for changes in the immune response to influenza vaccination and provide important information for the rational development of new vaccines, taking into account the individual characteristics of the immune response.

CONCLUSIONS

Thus, the analysis of antibody-formation showed that subjects with mutant genotypes of TLR-2, TLR-3, TLR-4 have a vaccinal response to administering vaccine against influenza at the level of patients with normal distribution of alleles of TLR, as evidenced by the achieved level of se-

roprotection, seroconversion and dynamics of geometric mean titers of antibodies on the 28th day of immunization.

Clinical and epidemiological efficacy of vaccination for patients with polymorphisms Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes is characterized by: a decrease in ARI cases in the postvaccinal period by 2-3 times; prevention of pneumonia in vaccinated subjects; decrease in the frequency of bronchitis by 2,5-3,8 times.

Individuals with polymorphic modified genotypes of TLR-2, TLR-3, and TLR-4 without other risk factors for influenza complications must undergo specific immunoprophylaxis as an effective method of preventing complications by inflammatory processes of lower airways.

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The article is part of the research work «Optimization of preventive measures for influenza in patients with polymorphisms Arg753Gln of TLR-2, Leu412Phe of TLR-3, Asp299Gly of TLR-4 genes».

ORCID and contributionship:
Nataliia O. Pryimenko: 0000-0002-8265-1143 [B, C, D]
Tetiana M. Kotelevska: 0000-0001-7508-4876 [B]
Tetiana I. Koval: 0000-0003-2685-8665 [F]
Vadym A. Bodnar: 0000-0002-1277-9344 [E]
Liudmyla M. Syzova: 0000-0002-8335-3295 [A, E]
Stanislav S. Rudenko: 0000-0002-9497-6703 [A]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Nataliia O. Pryimenko
Ukrainian Medical Stomatological Academy
22 Pershotravnevyi st., 36011 Poltava, Ukraine
tel: +38 0532 50 27 01
e-mail: pno.i@ukr.net

Received: 28.10.2019
Accepted: 07.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

EFFECTIVENESS OF PHYSICAL THERAPY IN MYOFASCIAL SYNDROME IN PATIENTS WITH MULTIPLE SCLEROSIS

DOI: 10.36740/WLek202009210

Zinovyi M. Ostapyak[1], Bogdan M. Mytckan[1], Przemyslaw Bejga[2], Roman P. Gerich[1], Serg L. Popel'[1]
[1] VASYL STEFANYK PRECARPATHIAN NATIONAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE
[2] UNIVERSITY OF ZIELONA GÓRA, ZIELONA GÓRA, POLAND

ABSTRACT

The aim: Is to conduct a comparative analysis of electroneuromyographic parameters in patients with myofascial pain syndrome with multiple sclerosis under the conditions of using various means of physical therapy.

Materials and methods: 105 patients aged 21 to 54 years were examined with MPS in MS. Neurological disorders were verified according to ENMG examinations. 64 patients were enrolled in an experimental group for which a specially designed program was included, which included reflexology and exercise for stretching muscles for 30 days. The control group included 41 patients who underwent a FT course based on therapeutic massage during the same time. Analysis of global ENMG was performed according to functional tests («muscle relaxation» and «maximum arbitrary muscle tension» with m. Tibialis anterior and m. Rectus femoris), M-responses and H-reflexes, polysynaptic responses (PSV) in withdrawal from these muscles during short-term stimulation n. plantaris (number of pulses in series 10, frequency - 20 Hz, duration of a separate stimulation signal - 1 ms, intensity - double threshold of contractile response of the muscles of the sole of the foot) and residual latency as the time of motor impulse on terminal non-myelinated nerve. Testing was performed on the same muscle groups on the left and righ.

Results: Before physical therapy during electromyographic testing, a significant decrease in the amplitude of the maximum M response, a decrease in the speed of the impulse in the proximal and distal segments of the peripheral nerve, was found to be significant compared with the control, the ratio of the proximal-distal coefficient and the residual latency index significantly increased, which indicates a demyelinating character lesions of nerve conductors. After reflexotherapy with muscle stretching in 38.0% of the patients of the experimental group, the dynamics of the amplitude of the M-answers on the left and on the right has only a tendency to further increase, while in the other 62.0% of patients, the amplitude of the M-responses increases bilaterally and is 65.7% higher than in the control group.

Conclusions: The use of reflexology in conjunction with stretching leads to a reduction in muscle spasticity and pain, as evidenced by electrophysiological indicators that substantiate their feasibility in the practice of physical therapy to improve the functional status of patients with MPS in MS.

KEY WORDS: multiple sclerosis, myofascial pain syndrome, electroneuromyographic, reflexology, stretching

Wiad Lek. 2020;73(9 p. II):1950-1957

INTRODUCTION

To date, multiple sclerosis (MS) remains a severe disease with wavy currents, periods of exacerbation, and partial remission [1,2]. Its medico-social importance is determined primarily by the development of early and persistent disability [3,4]. Numerous studies have found that within the first five years from the onset of MS, half of patients lose their ability to work, and when the disease lasts up to 10 years, their number is almost 2/3 of all patients with this diagnosis [5,6,7]. Despite the existence of a large number of publications, there are many problems in the etiopathogenetic theory of myofascial pain syndrome (MPS) in MS, without which further progress in the diagnosis and treatment of this disease is impossible [8,9,10]. The "white spots" about the causes of MPS in MS were highlighted, and it allowed us to show directions for further research, the results of which allow us to optimize existing diagnostic and therapeutic methods, especially for the development of modern pathogenetically substantiated physical therapy regimens and programs [11].

In recent years, the prevalence of MPS in MS throughout the world has significantly increased [12,13]. This is due both to a true increase in the incidence rate of MS, and to an improvement in diagnostic methods with the widespread introduction of modern neuroimaging methods of research into neurological practice that can detect diseases in the early stages of development [14,15,16].

The accumulated knowledge about the pathogenesis of MPS in MS in recent years may lead to the development of effective methods of prevention and treatment in the near future. [17,18].

Existing methods of treatment allow, with varying degrees of effectiveness, to reduce the risk of exacerbations, slow down the progression of the disease, and delay disability [19,20]. Despite some progress, the problem of treatment of MPS in MS requires further detailed study. In this case, it is necessary to conduct large-scale randomized trials of new drugs, check and confirm the results of experimental clinical studies [21,22], which is associated with

Table I. Electroneuromyographic parameters of patients before and after the introduction of a physical therapy program compared with the control group (x±SE)

Parameter	Before		After	
	EG	CG	EG	CG
Amplitude of the M response, μV	6,75±0,23	6,73±0,31	8,31±1,01*♯	7,02±0,76
SIprox., m/s	49,21±1,05	49,11±1,05	65,72±1,88*♯	53,07±1,43
SIdist., m/s	39,24±0,62	39,25±0,59	61,02±1,74*♯	49,59±1,47*
Proximal-distal coefficient	0,88±0,04	0,87±0,03	1,27±0,03*♯	1,12±0,02*
Residual latency, ms	3,09±0,151	3,07±0,11	1,66±0,04*♯	2,08±0,04*

Notes: * significant difference compared with indicators before starting physical therapy at $p < 0.05$; ♯ a significant difference compared with the control group at $p<0,05$.

the expenditure of large financial and human resources. Therefore, physical therapy (FT) is gaining importance, which has few contraindications and possible complications [17,18]. The most common means of FT are exercise and various physical factors [23].

The use of physical exercises for the symptoms associated with pain in the lower back and lower extremities in MS is determined by practical requests for a theoretical justification for their use in order to correct the functional state of the neuromuscular system in this category of patients.

In the specialized literature [8], only a few works relate to the estimation of the amplitude-frequency characteristics of the reflex excitability of spinal motor neurons in MPS in combination with MS. However, this is very important, because simple reflexes along a monosynaptic reflex arc that affect the manifestation of voluntary motor activity are realized through them. Therefore, the data of electroneuromyographic (ENMG) studies on the effect of FT contribute to a deeper and more comprehensive understanding of the mechanisms for organizing responses at the spinal and peripheral motor levels. At the same time, multisynaptic testing allows us to assess the level of reflex excitability of muscles to which the appropriate FT methods are used in patients with MPS in MS.

THE AIM

The aim of the article is to conduct a comparative analysis of electroneuromyographic parameters in patients with myofascial pain syndrome with multiple sclerosis under the conditions of using various means of physical therapy.

MATERIALS AND METHODS

105 patients aged 21 to 54 years, who were admitted to the neurological department with the diagnosis of IFS in MS were examined. In all examined patients, at admission clinically diagnosed neurological disorders (lower mixed-type paraparesis) of varying severity, which were verified according to the ENMG-survey using global and stimulating methods.

Of these, 64 patients comprised an experimental group (EG) for which a specially designed program was used, which included reflexology and physical exercises to stretch muscles for 30 days.

The control group (CG) included 41 patients with MFBS in MS who underwent a course of FT, which is based on therapeutic massage for the same time [9].

The electromyographic (EMG) study was performed on a 2-channel computer Neuro-EMG-Micro (NEURO-SOFT, Russia). The complex of methods included registration and analysis of the global (total) ENMG (functional tests: "muscle relaxation" and "maximum voluntary muscle tension" with m. Tibialis anterior and m. Rectus femoris), M-responses and H-reflexes, polysynaptic responses (PSV) during abduction from these muscles with short-term stimulation n. plantaris (the number of pulses in a series of 10, the frequency is 20 Hz, the duration of a single stimulation signal is 1 ms, the intensity is the double threshold of the contractile response of the muscles of the plantar surface of the foot) and residual latency as the time of the motor pulse along the terminal non-myelinated nerve fibers. Testing was carried out on the same muscle groups on the left and right.

The examinations were conducted directly upon admission to the neurological department and after 20 and 30 sessions after the start of the FT program.

Patients underwent appropriate clinical and neurological examination and specific manual-therapeutic diagnostics [8]. The severity of pain was determined on a visual-analogue scale (VAS) and the scale of life disorders Kurtzke (EDSS), and the degree of severity of chronic pain and its impact on social maladaptation was evaluated by Van Korf's questionnaire [9].

Statistical data processing was carried out using the Microsoft EXEL-2003 data package, supplemented with non-parametric statistics and distribution normality estimation statistics "Statistika-6".

RESULTS

Clinical studies have established that in 95.0% of patients with MBS in MS, the severity of pain according to YOUR is 6.0 ± 0.03 points, and according to EDSS - 4.0 ± 0.02 points. At the same time, the intensity of pain and the degree of social maladaptation according to the Van Corf questionnaire are 65 and 67 points, respectively, which refers to the second class of chronic pain.

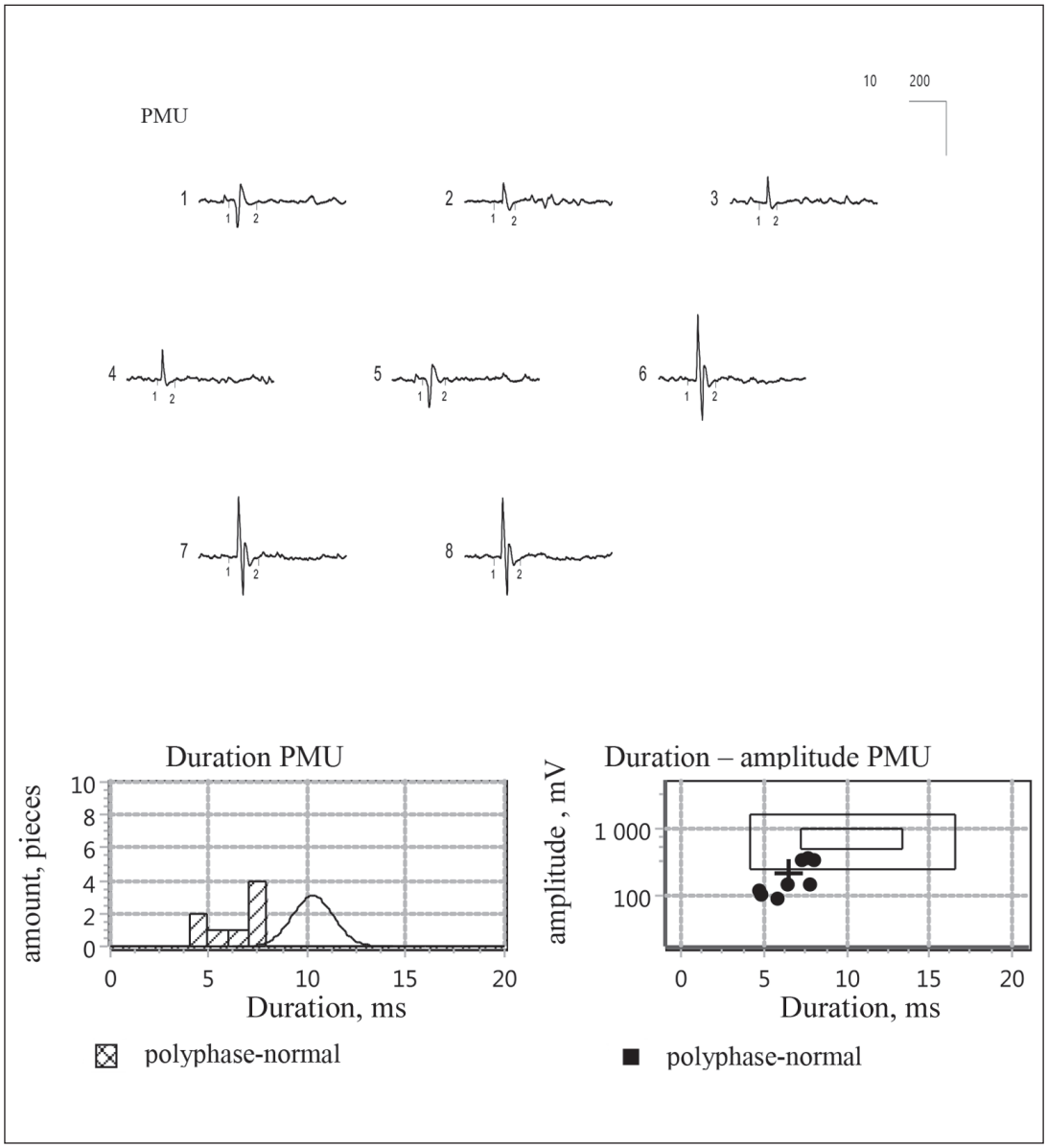

Fig. 1. Characterization of the potential of motor units in patients of the control group after the course of physical therapy according to the program of therapeutic massage.

When analyzing the results of stimulating ENMG, probable changes in the electrophysiological parameters characterizing the condition of the peripheral nerve conductors of the lower limb appear and are presented as average values in the table. 1. Survey data before FT indicate the presence of some features in the neurophysiological status of the sensorimotor innervation of the lower extremities in all patients with MS.

During ENMG testing, a significant decrease in the maximum amplitude of the M-response, a decrease in the speed of the impulse (SI) in the proximal and distal segments of the peripheral nerve, was found to be significant compared with the control, the ratio of the proximal-distal coefficient and the residual latency index significantly increased, which testified to the demyelinating nature of nerve damage conductors (see table I).

In particular, the average amplitude of the total EMG (test - "maximum arbitrary voltage") in individual leads was significantly lower than the reference values (on average by 43.2%, $p < 0.05$). For example, the average amplitude of the total EMG m. rectus femoris of the right and left lower extremities was 6.85 μV and 6.64 μV, respectively (61.0% and 83.0% of the reference values), the value of m. tibialis anterior left and right lower extremities were 6.79 μV and 6.66 μV (44.5% and 55.0% of the reference values).

After the introduction of the FT program with the use of reflexology in combination with muscle stretching, a bilateral increase in the amplitude of the total ENMG by an average of 23.4% of the values was noted, prior to FT.

Compared with the examination data before FT in patients with CG in whom only therapeutic massage was performed, a statistically unreliable bilateral increase in the amplitude of the total ENMG was noted.

In EG patients with whom acupuncture was performed without muscle tension, the N-reflex on the left was 3.4 μV

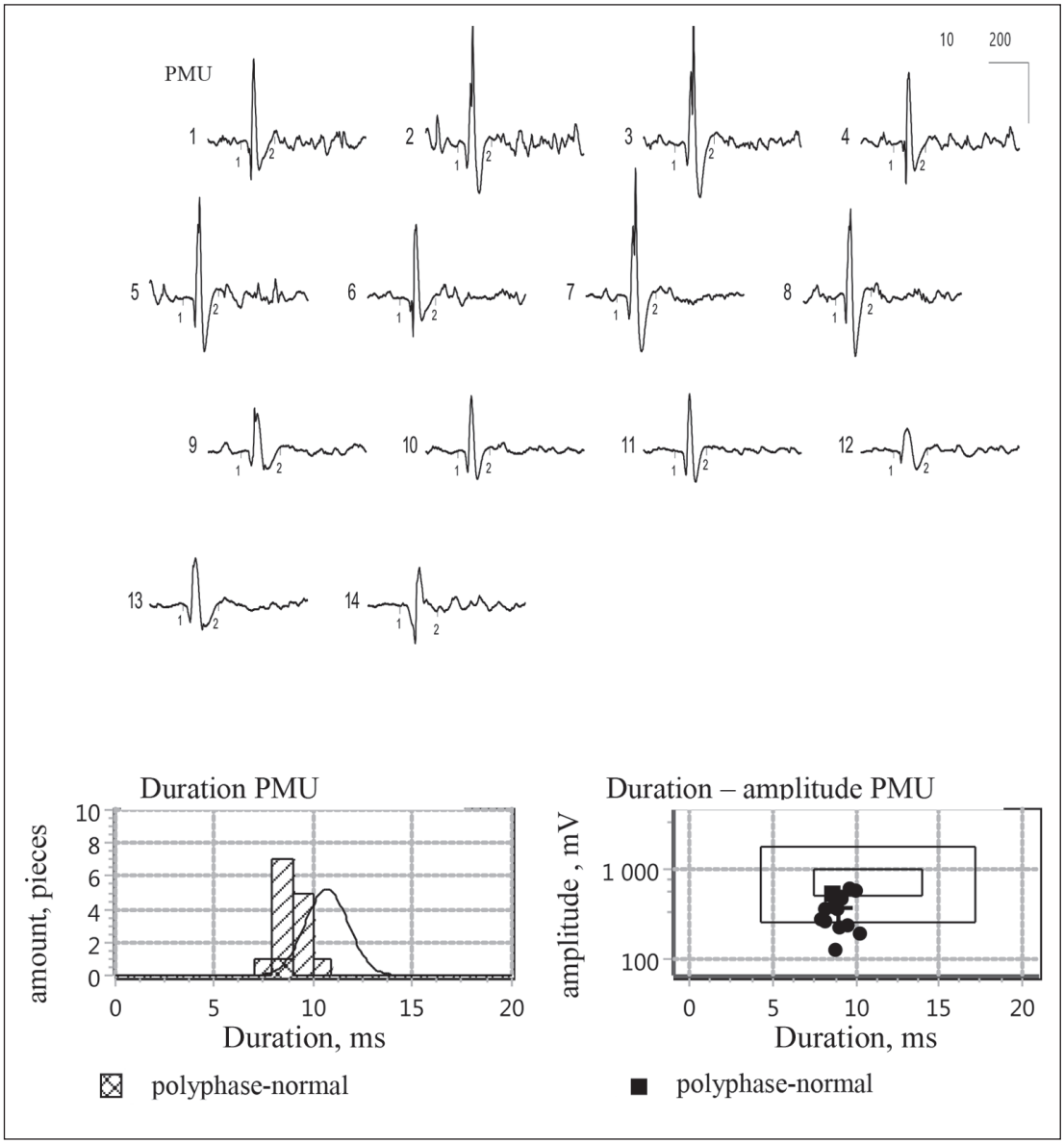

Fig. 2. Characterization of the potential of motor units in patients of the experimental group after the course of physical therapy.

(47.0% of the control values) and the duration of the evoked potentials on the left was 3.1 mV and 3.0 μV on the right were slightly lower than the control values (respectively 12,0% i 15,0%).

In this case, compared to the values up to FT, the amplitude of the H-reflex in the drainage from m is statistically significant ($p < 0.05$), tibialis anterior increased by an average of 14.2%, indicating a demyelinating nature of nerve fiber damage [20,24].

The exception was patients with CG, in whom, after FT using only therapeutic massage, a mono- or bilateral decrease in the amplitude of the H-reflex was noted by 47.8% and 42.0%, respectively ($p < 0.05$). Moreover, in all patients with CG in most leads, a decrease in the amplitude of M responses to an average of 82.7% of the magnitude before FT was noted, especially clearly reflected in the dynamics of the corresponding indicator in the lead from m. tibialis anterior.

In particular, the amplitude of the total ENMG allocated to m. tibialis anterior on the left decreased from 6.7 mV to 0.6 mV, which amounted to 90.0% of the values to the FT value, while latency increased from 25.6 ms to 40.3 ms (157.4% of the value to FT).

In all patients with MS before FT, the amplitude of the total ENMH of the left and right limbs during the period was 3.1 mV and 3.0 mV, respectively, and after FT decreased to 0.2 mV and 0.3 mV (6.5% and 10.0 %), while latency increased from 26 ms and 23 ms to 41 ms and 40 ms (157.7% and 173.9% of the reference values, respectively).

A quantitative analysis of the main fluctuations of the global ENMG revealed in most cases (90.0%) a clear asymmetry in the amplitude characteristic.

It should be noted that in 45.0% of patients with a high total score on the EDSS scale (6.5), the asymmetry of the

amplitudes of the total ENMG (maximum 80.0%) was also maximum for two muscle groups.

At the end of FT using acupuncture with muscle stretching in 38.0% of patients with EG in the lead from m. tibialis anterior dynamics of the amplitude of M-responses on the left and on the right has only a tendency to further increase, while in the other 62.0% of patients, the amplitude of the M-response is m. tibialis anterior bilaterally increased on average to 70.4% of the value that was observed upon admission to the hospital and was 65.7% higher than in the CG.

The knowledge of the interference pattern distinguished different potentials of motor units (PMU). In patients with CG, deviations from reference PMU duration were significantly ($p < 0.01$) greater. Moreover, the duration of PMU is less than in patients with EG (-3.62 ± 0.14 i - 4.15 ± 0.17, respectively) (Fig. 1).

At the same time, the deviation of the amplitude PMU in the EG is significantly ($p < 0.001$) less than in the patients with CG (+295.1 ± 1.23 and + 132.2 ± 0.84 respectively) (Fig. 2).

DISCUSSION

After analyzing the data of scientific sources [8,21] and studying the topographic and anatomical details of various parts of the spine in patients with MS [25,26], it can be argued that the cause of pain in lumbar localization is compensatory overstrain of the myofascial system, as a response to inadequate nerve impulses, which is a result of demyelination , and in some cases also axonopathies [6], which are confirmed by ENMG indicators.

The presence of subclinical variants of peripheral nervous system lesions, manifested only by ENMG methods, is shown, which must be taken into account when conducting FT [10,27].

After a 20-day course of FT, 70.0% of EG patients had positive clinical dynamics. Mild pain syndrome remained in only 30.0% of patients. In this case, pain appears only with a sharp transition from one body position to another, but was completely absent in a calm lying position and with moderate movements or a short stay on legs.

The method we used was especially effective for acute pain in the early days of FT. In the future, the integrated use of reflexology and muscle tension in the EG allowed: to reduce pain to minimum levels after 10 sessions; to restore indicators that affect the improvement of vital activity in Kurtzka after 20 sessions, which made it possible to more effectively reduce the severity of chronic pain and its effect on social maladaptation in the same period.

Moreover, already from the 20th session, a stably low level of spasticity m was established. tibialis ant. and m. rectus femoris, and in the CG, a decrease in the level of tonic tension of these muscles was achieved only after a 30-day session of therapeutic massage according to the traditional treatment regimen for MS.

Assessment of electrophysiological and psychometric disorders in patients with MPS in MS showed that, prior to FT, an increase in the average amplitude and a decrease in the average duration of missile defense may correspond, firstly, to an increase in the excitation of α-motor neurons, which is associated with a decrease in inhibitory effects on spinal motor neurons and interneurons in combination defeat of the pyramidal and extrapyramidal paths. In a different way, everything can be connected with the structure of the segmental apparatus of the spinal cord and skeletal organs, which is connected with the trivial nature of the disease. For the sake of processing, we need to bring them to the structurally functional functions of the fibers. In its entirety, the biomechanical component of spasticity and the regular manifestation in psychometric indicators show that the intensity of the pain syndrome and the level of social disadaptation.

Myofacial triggering points and refining in general, hereby created and massive proprioceptive afferents in the segmental structure of the central nervous system.

The above facts regarding the reduction of latency and stabilization of the duration of the H-reflex testify to the shortening of the path of its realization with the closure at the level of the caudal department of the brain stem on the side of the predominance of MPS. As the role of the communicative capacity of brainstem interneurons increased, the duration of the M-response was to increase. The reflection of the increased excitability of brainstem interneurons is a decrease in the threshold and latency period, an increase in the amplitude of the ENMG indicators.

The results obtained objectively characterize the failure of the inhibitory mechanisms in the central nervous system and the functional deficiency of the antinociceptive system in MS. The weakness of the inhibitory processes leads to the facilitation of sensory inputs for streams of peripheral afferentation and leads to the formation of generators of pathologically enhanced excitation in the efferent systems of the brain [2].

Our neuronal activity reflects the interaction of nociceptive and antinociceptive systems that are implemented by brain stem structures.

In patients with predominance of pain due to the involvement of muscles of one half of the body and the predominant involvement of the lower extremity, an increase in the maximum amplitude and area of the H-reflex, the H/M index, the increase of the H-reflex was noted. Increase in amplitude of H-reflex [3], increase of H/M [12,23] indicate a decrease in supraspinal impact, since in this case the excitability of the motor neuron pool increases and their synchronization increases. H-reflex amplification is not only dependent on the activity of spinal nociceptive neurons, but is also associated with the activation of supraspinal centers involved in the perception and analysis of "pain" signals and coordinating reflex muscle response in MS [2].

Thus, when MPS is strengthened, both due to the involvement of the half-body muscles and the predominant involvement of the muscles of the lower extremity, the level of segmental excitability of the spinal cord is increased. Direct correlation relationships of lower body MPS severity

with H-reflex rates reflect activation of spinal motoneurons. The direct correlation between the severity of myofascial half-body pain with the predominant involvement of the lower extremity muscles and the H-reflex indexes also indicate the activation of the supraspinal nociceptive centers.

CONCLUSIONS

1. The use of reflexology in combination with stretching is a highly effective effect on the number of positive results in reducing muscle spasticity (47.0% of the total number of patients), reducing the severity of pain (64.5% of patients) and reducing the degree of exposure to chronic pain. to the level of social maladaptation (in 60.3% of patients with MPS in MS).
2. The results of the study, focused on the evaluation of electrophysiological characteristics of severity and dynamics of the development of myofascial pain syndrome and neurological deficiency due to multiple sclerosis, indicate the feasibility of monitoring the function of the root-segmental structures and corticospinal tracts.
3. Our proposed version of the specialized package of electromyromyographic techniques is easy to implement and is sufficiently high reproducible and informative of selected indicators.
4. The results obtained provide a justification for putting into practice physical therapy daily (within 30 days) acupuncture stimulation of the lower extremity muscle anti-gravity group while simultaneously stretching them as an adequate method of improving the functional status of patients with MPS in MS.

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ORCID and contributionship:
Zinovyi M. Ostapyak: 0000-0001-7687-161X [A, D, F]
Bogdan M. Mytckan: 0000-0002-5853-713x [E, F]
Przemyslaw Bejga: 0000-0003-4871-4689 [A, F]
Roman P. Gerich: 0000-0003-4527-4972 [B, F]
Serg L. Popel': 0000-0001-9019-3966 [B, C, F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Zinovyi M. Ostapyak
Vasyl Stefanyk Precarpathian National University
57 Shevchenka str., 76025 Ivano-Frankivsk, Ukraine
tel: +380965782295
e-mail: zinoviy6@ukr.net

Received: 21.11.2019
Accepted: 29.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

THE CAUSES OF ADVERSE TREATMENT RESULTS AND THE WAYS OF THEIR ELIMINATION IN BLEEDING FROM CHRONIC GASTRODUODENAL ULCERS

DOI: 10.36740/WLek202009211

Gennady E. Samoilenko, Stanislav O. Zharikov, Ruslan P. Klimanskyi
DONETSK NATIONAL MEDICAL UNIVERSITY, LYMAN, UKRAINE

ABSTRACT

The aim: is to determine the main causes of adverse outcomes of the patients' treatment with acute ulcerative gastroduodenal bleeding and to develop preventive measures to improve the quality of the patients' treatment with this pathology.

Materials and methods: A retrospective analysis of the treatment results of 1323 patients with bleeding of ulcerative etiology has been carried out. There are 375 patients with gastric ulcer (28.3%) and 948 patients (71.7%) with duodenal ulcer among them. The patients' age ranged from 15 to 93 years old. Concomitant pathology was observed in 623 (47.1%) patients, the most common of which were coronary heart disease, chronic non-specific lung diseases and cerebrovascular diseases. Mild severity of blood loss was detected in 404 (30.5%) patients, moderate severity 693 (52.5%), severe 145 (10.9%) and extremely severe 81 (6.1%). Overall mortality was 5.9%, postoperative mortality 6.3%, the mortality in conservative treatment only 6.1%.

Results: The main cause of the patients' mortality with acute ulcerative gastroduodenal bleeding was decompensated hemorrhagic shock which developed at the prehospital stage in 45.3% and as a result of bleeding recurrence during treatment 44.2% of the patients. Inadequate drug therapy increases the risk of bleeding recurrence from 15.8 to 32.7%. The use of proton pump blockers and the combination of bolus and prolonged use of proton pump blockers allow to reduce the risk of bleeding recurrence by half (up to 6.8%).

Conclusions: Endoscopic hemostasis in combination with the injection method with diathermocoagulation or thermal coagulation can be considered as full-fledged, and when performing endoscopic monitoring the preference should be given to coagulation methods of diathermo- and hydrodietermocoagulation.

KEY WORDS: peptic ulcer, bleeding recurrence, diagnosis, treatment, endoscopic hemostasis

Wiad Lek. 2020;73(9 p. II):1957-1961

INTRODUCTION

The problem of acute ulcerative gastroduodenal bleeding (AUGDB) has been an urgent public health problem for more than 150 years. According to the decision of Maastricht group despite the fact that specific eradication therapy of Helicobacter pylori has been introduced into daily medical practice widely, the number of complications of peptic ulcer in the form of bleeding has a steady upward trend. So, according to the Ministry of Health of Ukraine the largest increase in the cases of ulcerative bleeding in our country has occurred over the past 5 years [1, 2, 3].

Indeed, there is a decrease in the total number of surgical interventions for peptic ulcer disease but it primarily applies to planned surgical interventions for the treatment of peptic ulcer. Despite significant progress in the development of endoscopic and pharmacological technologies the proportion of the operations to stop ulcer bleeding remains constant even in developed countries of the world. According to some foreign and native authors there is a change in nosological forms in bleeding from the upper gastrointestinal tract – displacing of other diseases due to the growth of ulcerative bleeding from (50.5 ± 7.2) to (63.7 ± 8.4) % of the cases [4, 5, 6].

Over the past 10 years thanks to the rapid development of endoscopic technologies in our country and CIS countries significant differences have been revealed in the clinical and endoscopic characteristics of ulcer bleeding compared with the countries of Europe and America, the Near and Far East. Thus, according to American scientists' data there has been an increase in the number of the cases with complicated course of peptic ulcer by 20% over the past decade. 20 million people suffer from peptic ulcer in the United States and about 100000 patients are operated on annually and 6000 people die from various complications of this severe systemic disease [7, 8, 9].

THE AIM

The aim of the study is to determine the main causes of adverse outcomes in the patients' treatment with AUGDB and to develop preventive measures in order to improve the quality of the patients' treatment with this pathology.

MATERIALS AND METHODS

To achieve the goal of the study we carried out the retrospective analysis of the results of the treatment of 1323 patients with bleeding of ulcer etiology who were admitted to the surgery and endoscopy clinic of Donetsk National

Table I. The main indicators of the patients' treatment with acute ulcerative gastroduodenal bleeding for the period from 2015 to 2018

Main characteristics	The patients' number (%)	Died	
		Abs.	%
A total of the patients:	1323 (100%)	79	5,9%
stomach ulcer	375 (28.3%)	32	8,5%
duodenal ulcer	948 (71.7%)	47	4,9%
Operated:	268 (20.3%)	17	6,3%
at the height of bleeding	16 (5.9%)	3	18,8%
due to bleeding recurrence	52 (19.5%)	8	15,4%
due to unstable hemostasis	79 (29.5%)	5	6,3%
Planned before	121 (45.1%)	1	0,8%
Not operated	1055 (79.7%)	64	6,1%

Medical University at the central city clinical hospital in Druzhkovka for the period from 2015 to 2018. The patients' age ranged from 15 to 93 years old. At the age of 20 years there were 39 (2.9%) patients, from 20 to 45 years old 428 (32.4%), from 46 to 60 years old 380 (28.7%), from 61 to 74 years old 372 (28.1%) and over 75 years old 104 (7.9%).

A significant relationship was found between chronic ulcerative bleeding and the presence of concomitant pathology while analyzing concomitant pathology. A combination of two or more diseases was observed in 623 (47.1%) patients with concomitant pathology, the most common of which were coronary heart disease, chronic non-specific lung diseases, cerebrovascular diseases and diabetes mellitus. In addition, there were 34 (5.5%) patients with decompensated liver cirrhosis with the manifestations of liver failure and 15 (2.4%) patients with chronic renal failure in this group.

Overall mortality was 5.9%, postoperative mortality 6.3%, mortality with conservative treatment alone 6.1%.

The duration of the prehospital period ranged from 1 hour to 21 days. In the first 24 hours from the onset of the first signs of bleeding 721 (54.5%) patients were admitted, in the period from 25 to 72 hours 210 (15.9%), more than 72 hours 389 (29.4%). Mild severity of blood loss was detected in 404 (30.5%) patients, moderate severity 693 (52.5%), severe 145 (10.9%) and extremely severe 81 (6.1%). The ulcer was localized in 375 (28.3%) patients in the stomach, and in the duodenum in 948 (71.7%).

The main indicators of the patients' treatment with AUGDB are presented in table I.

RESULTS

Analyzing the reasons for unsatisfactory results of the patients' treatment several factors should be noted, the influence of which undoubtedly led to a lethal outcome. Unfortunately, not all the components of the course of the disease were able to be influenced actively. To facilitate the systematization of adverse factors it was decided to divide them into two main categories: objective and subjective.

The duration of the prehospital period, the intensity of bleeding, the degree of the compensation of concomitant pathology, topographic features of the source of bleeding and also such a factor as the patient's refusal to undergo treatment (both drug and endoscopic) were referred to the first category of the factors that we were not able to influence.

The category of subjective factors includes the diagnostic value of the primary endoscopic examination, medical manipulations both at the first stage and in the process of medical monitoring, the compliance with tactical settings and the usefulness of drug therapy.

Contrary to the expectations the continuation of the prehospital stage did not affect the unfavorable prognosis of the course of the disease significantly. All things being equal, the mortality rate among the patients hospitalized in the first 12 hours from the onset of the first signs of bleeding was the highest (8.5%) and as the time increased it had a clear tendency to decrease to 4.8% after 48 hours. This factor, perhaps, cannot be decisive in terms of predicting an adverse outcome of the disease. The degree of blood loss had a significant effect. There was a steady increase in mortality from 0.7% with mild blood loss to 39% with extremely severe blood loss.

Acute gastroduodenal ulcers associated with the drug usage were diagnosed in 251 patients (18.9%) and recently accounted for a third of the causes of gastroduodenal bleeding in elderly patients. According to our materials it is the second most frequent cause of the complications of acute ulcers in inpatients. For the most part, these ulcers appear after taking cyclooxygenase inhibitors. In this group there were 159 patients (63.3%) aged over 65 years old with cardiovascular disease and they took more than 3 drugs a day, usually disaggregants (acetylsalicylic acid), anticoagulants (warfarin), non-steroidal anti-inflammatory drugs (diclofenac). The combination of dyspepsia symptoms with the constant use of disaggregants increases the risk of developing acute ulcers in 2 times. In addition, we also included the risk factors for the development of such gastropathies as old age, the presence of ulcerative history, decompensated forms of concomitant diseases (cardiovascular, cerebrovascular, diabetes mellitus), decreased physical activity, simul-

taneous taking of anticoagulants, glucocorticosteroids and non-steroidal anti-inflammatory drugs.

The risk of the development of erosive and ulcerative lesions of the gastrointestinal tract increases in 2 times with the combination of 2 or more of these factors. In 75-90% of cases they are complicated by gastrointestinal bleeding.

Thus, having analyzed the patients' data of the study group we attributed old age, decreased physical activity, II-III degree of organ dysfunction according to the severity of APACHE and MODS scales and the use of medications to the risk factors after the complications from chronic gastroduodenal ulcers. So, when these adverse factors are detected in patients, erosive and ulcerative lesions of the gastrointestinal tract should be prevented.

The indicator of the mean blood pressure was of great importance. At the initial numbers up to 40 mmHg the mortality was 35.3%, at 41-60 mm Hg. 28.2%, at 61-80 mmHg 10.5%, at 81-100 mm Hg 3.9% and at 100 mmHg and higher 3.8%.

The total mortality rate in the group of the patients with bleeding from chronic ulcers of the stomach and duodenum was 6.1% (64 patients).

29 patients (45.3%) of that number were hospitalized in a state of irreversible hemorrhagic shock who were in the intensive care unit from 10 minutes. up to 1 day. Despite the treatment the patients' condition got worse progressively. Apparently, we were not able to help this category of the patients that, unfortunately, allowed us to attribute them to prognostically adverse effects of the treatment. We assigned one patient who was operated on an emergency basis at the height of bleeding to the same group. Despite providing surgical treatment and infusion therapy on the operating table it was not possible to remove the patient from the state of hemorrhagic shock. Unpredictable adverse effects of the treatment included 5 patients (1.9%). All patients underwent surgical intervention based on the indications, however, in the postoperative period pancreatic necrosis (4 patients) and pulmonary embolism (1 patient) developed.

In 31 patients (48.4%) the direct cause of death was the decompensation of somatic pathology which developed against the background of severe posthemorrhagic anemia. All these patients did not receive adequate medication.

As can be seen from the study, the greatest impact on the development of an adverse outcome of the disease had bleeding recurrence (BR). BR was detected in 52 patients (19.5%). As a consequence of BR the phenomenon of hemorrhagic shock developed in 23 patients (44.2%) and it was the direct cause of their death. BR of these patients had clinical manifestations such as repeated vomiting of blood, melena, decreased blood pressure, loss of consciousness. Among them there were 8 patients (34.8%) operated on the emergency basis, the remaining 15 patients (65.2%) did not have any surgery. In 4 patients (7.7%) BR led to decompensation of somatic pathology and death. In 7 patients (13.5%) clinical manifestations were absent, however, the fact of repeated bleeding led to the need to change the treatment tactics. The forced surgical treatment that was started against the background of posthemorrhagic anemia can be considered a tactical mistake. As a consequence of it there was the development of postoperative complications in the form of insolvency of the anastomosis, DIC, etc.

Thus, BR is a major factor in the development of adverse effects of treatment. Surgical intervention performed by force against the background of severe anemia and decompensation of somatic pathology is not a method of choice and it is accompanied by high mortality. In the table above, high mortality rates during the operations at bleeding height — 18.8% and in connection with BR — 15.4% are noteworthy. At the same time the mortality rate after the operations that were performed after stabilization is almost 3 times lower and in the planned order it does not reach 1%. So, the main task facing the team of the specialists is the prevention of bleeding recurrence.

DISCUSSION

Several factors influence the occurrence of BR such as the degree of blood loss, topography, the size and depth of the ulcer defect, the usefulness of antisecretory drug therapy (ADT) and endoscopic prophylaxis of bleeding recurrence (EPBR). In particular, the least likelihood of bleeding recurrence was noted with stomach ulcers less than 1.5 cm in diameter and with duodenal ulcers less than 1 cm in diameter. In this case as the size of the ulcers increases the frequency of bleeding recurrence rises. In this regard especially dangerous are giant ulcers (the stomach more than 3 cm in diameter, the duodenum more than 2 cm in diameter). The likelihood of bleeding recurrence is significantly higher with deep ulcers and especially with stenosis of the pyloroduodenal segment that is not passable for an endoscope. The latter concerns duodenal ulcers.

Currently, the use of proton pump blockers is considered a priority form of ADT. The use of these drugs according to the traditional scheme is accompanied by BR in 15.8% of the patients. The absence or inferiority of drug therapy almost doubles the risk of bleeding recurrence to 32.7%. At the same time the combination of bolus and prolonged use of proton pump blockers (80 mg IV bolus, then 8 mg/h for 2-3 days) reduces the risk of bleeding to 6.8%.

We always began arresting of prolonged bleeding with perivasal and periulcerous administration of vasoconstrictors and procoagulants. As a rule, the introduction of the so-called "hemostatic mixture" made it possible to stop the initial continued bleeding in 75.4% of patients within 3-5 minutes from the beginning of the manipulation. 11.7% of the patients suffered from hemostasis which in result of the usage of the physiological solution created the infiltration shaft around the defect and it did not require further electro- or thermocoagulation methods. The preference was given to periulcerous injections of physiological solution or glucose solution and the application of foam or film-forming preparations. The addition of vasoconstrictors to the mixture and the use of coagulation are considered advisable only if there is a high risk of bleeding recurrence. Control endoscopic examinations were performed according to the rules adopted for chronic ulcers.

The studies were performed every 4-12 hours until the signs of unreliable hemostasis disappeared. The higher the likelihood of bleeding recurrence the presence of a loose blood clot, large, protruding into the lumen, thrombosed vessels, hemorrhagic plaque at the bottom of the defect, the more often control studies are performed. It allows you to identify either bleeding recurrence at an earlier stage and carry out appropriate measures or perform preventive manipulations with a shorter interval between them to consolidate the result. Reducing the risk of bleeding recurrence that is determined during the control studies (the presence of small dark thrombosed vessels that do not protrude into the lumen, an increase in the layer of fibrinous plaque at the bottom of the defect) allows you to increase the interval between control studies and when performing the manipulations themselves it is possible to go to the most gentle methods – application of coagulating drugs, foaming or film-forming drugs. In this case, special attention is paid to the introduction of the drugs that create favorable conditions for more rapid relief of perifocal inflammation caused by underlying disease or resulting from previous manipulations. The absence of the signs of unreliable hemostasis is an indication for stopping endoscopic prophylaxis of bleeding recurrence.

An essential condition for the prevention of bleeding recurrence is high-quality and complete endoscopic therapy. Diagnostic errors during both the initial study and endoscopic monitoring lead to the wrong choice of treatment method. Thus, due to incorrect interpretation of BR data occurred in 17 operated patients (6.3%). Inadequate primary endoscopic hemostasis (EH) led to early BR in 7 patients (2.6%), inadequate EPBR at admission and during treatment monitoring led to the development of BR in 56 patients (20.9%). In other words, the examination technology compliance, correct interpretation of the data and full-fledged manipulations would most likely help to avoid BR in 29.8% of patients. Patients with continued bleeding should be assigned to a high-risk group for developing BR. To achieve stable hemostasis, especially in the cases when profuse bleeding is noted during the initial study, it is justified to use a combination of the injection method with diathermocoagulation (DC) and thermal coagulation (TC). Such a potentiated EH effect is equally both effective and reliable. While performing endoscopic monitoring the preference should be given to coagulation methods of diathermo- and hydrodiatermocoagulation.

As a rule, by the time EH was used the bleeding was arrested, however, the achieved hemostasis was considered unreliable as a loose blood clot was formed and there was no full confidence in the absence of blood leakage. When applying coagulation techniques we tried to avoid the contact of the distal end of the probe with the deep structures and the walls of the mucosal defect in order to avoid the disturbance of the unstable state of hemostasis and the development of deep destructive changes. We began coagulation from the periphery of the clot, gradually compacting it and reducing its volume. Coagulation was combined with gentle aspiration of the loose part of the clot and liquid blood or with the washing of the contents of the ulcer crater. We consider complete aspiration of the clot to be an irrational and dangerous measure. Electrocoagulation of a clot is quite a complex and precise manipulation that requires great care when being performed because of the possibility of "welding" of the clot to the diathermosonde. Recently, we have been actively using argon-plasma coagulation which is devoid of these negative properties. The advantages of the method include the absence of deep tissue damage, reliable and rapid coagulation of the clot. It was performed in 122 patients and we were convinced of the effectiveness of this method.

CONCLUSIONS

1. The main reason for the mortality of the patients with AUGDB was decompensated hemorrhagic shock that developed at the prehospital stage in 45.3% and 44.2% of the patients as a result of BR during their treatment.
2. Inadequate drug therapy increases the risk of bleeding recurrence from 15.8 to 32.7%. The use of proton pump blockers, the combination of bolus and prolonged use of proton pump blockers, allows reducing the risk of BR development (up to 6.8%) in half. Endoscopic hemostasis with the combination of the injection method with DC or TC can be considered full-fledged and when performing endoscopic monitoring the preference should be given to coagulation methods of diathermo-and hydrodiermacocoagulation.

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9. Abraham N.S. Novel oral anticoagulants and gastrointestinal bleeding: a case for cardiogastroenterology. Clin. Gastroenterol. Hepatology. 2013;11(4):324–328.

ORCID and contributionship:
Gennady E. Samoilenko: 0000-0003-0075-4307 [A, E, F]
Stanislav O. Zharikov: 0000-0001-6503-1068 [C]
Ruslan P. Klimanskyi: 0000-0002-9118-7813 [B, D]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Ruslan P. Klimanskyi
Donetsk National Medical University
39 Machinostroiteley st., 84313 Kramatorsk, Ukraine
tel: +380509038996
e-mail: ruslanmozg@gmail.com

Received: 08.11.2019
Accepted: 30.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

TOXICOLOGICAL AND MICROBIOLOGICAL ESTIMATION LEVEL OF POLLUTION ECOSYSTEMS IN THE INDUSTRIAL REGION OF UKRAINE – KRIVOY ROG CITY

DOI: 10.36740/WLek202009212

Luibov V. Hryhorenko, Svitlana Yu. Yehorova
DNIPROPETROVSK MEDICAL ACADEMY MINISTRY OF HEALTH OF UKRAINE, DNIPRO, UKRAINE

ABSTRACT

The aim: Scientific substantiation necessary of PMWW application for the ecologically safe formation of the secondary ecosystems in the mining and iron ore processing areas.
Materials and methods: Sanitary-chemical investigation of water samples (n=132); biological objects – plants and aquatic biota was conducted on the content of Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe (n=112); wild plants samples (n=135); sanitary-microbiological and parasitological indicators 1 – 3 years old waste water sludge (WWS) (n = 68).
Results: Overnormal concentrations of salt had been found in water samples, taken from the river Inhulets (2.1 MPL), sulfates and carbonates (2.7 MPL), iron (2.1 MPL), chloride (1.7 MPL), magnesium (3.1 MPL). In wells from nearest villages water is not suitable for drinking purposes and contains total sum of salts – 4.97 MPL, sulfates and carbonates – 5.16 MPL, cadmium – 3.7 MPL, lead – 1.53 MPL. Thus, the toxic heavy metals concentrations (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) in the fish and amphibians did not exceed the permissible levels.
Conclusions: Total pollution of the soil within six months after application of sludge correspond to the "permissible" level (Z_c=1.61). Use of clearing facilities sludge aged from 1.5 years old and of longer in the amount 15 kg/m^2 did not lead to increased concentration of heavy metals in the top layer of dumps.

KEY WORDS: mining area, wastewater treatment, sludges, pollution, contaminants, heavy metals, chemical and epidemiological safety

Wiad Lek. 2020;73(9 p. II):1962-1967

INTRODUCTION

Mining at the Eastern regions of Ukraine is accompanied by significant environmental shifts; there impact on the natural landscape could be compared to the historical geological processes in a geosphere [1]. In the area of mining and processing enterprises of Krivoy Rog (MPEK) – North, South, Inhulets and Central mining enterprises to the external dumps of quarries was carried out over 3700 ha of usable area and brought about 1000 ha of the nearest landfills [2]. Technogenic geosystems (quarries, dumps) are often contiguous with settlements in the city, but were not suitable for any use: their surface is dead, biodiversity is minimal, microclimatic conditions are far from natural. Majority of artificial landscapes formed as the result of waste storage mining, being the source of potential risk to the human health [3]. For natural transformation of these territories, and reproduction of biodiversity, mostly constrained by an acute shortage of nutrients in the dead soil, should necessary 30 – 50 years, while anthropogenic landscape will adversely affect on the located areas [4-6]. Artificial acceleration natural processes of rehabilitation of man-made landscapes due to the exogenous supply of organic matter provides the opportunity to reduce their environmental risks and return recreational use of the large areas near the cities. Perspective should become usage of the waste utilities – precipitation of the municipal wastewater (PMWW), which is based on a safe and economical disposal method. PMWW contain a significant amount (50-70 %) of plant nutrients - humphry organic substances, but last time they did not used in the agriculture due to the heavy metal compounds [7] and sources of the infectious and viral diseases [8]. Every year on the sewage treatment facilities in major of industrial cities of Ukraine produced about 1 million m^3 of precipitation. Majority of these treatment facilities (about 2 thousand) is situated in Dnipropetrovsk region – 18 %, more than other regions of Ukraine [9]. Waste water sludge (WWS) is a constant source of the soil, surface and underground waters, atmospheric air contamination with hydrogen sulfide, ammonia, gaseous products of putrefaction of proteins. Further expansion of sludge areas due to the increase of lands is impossible, therefore, disposal of sludge for the numerous cities in Ukraine is an urgent ecological and hygienic problem [10].

THE AIM

Scientific substantiation necessary of PMWW application for the ecologically safe formation of the secondary ecosystems in the mining and iron ore processing areas.

MATERIALS AND METHODS

It was research non recultivated waste dumps in Krivoy Rog mining and processing enterprises (MPE) as the dangerous objects, which adversely affect to the all bordering territories. We carried out water samples, taken from river

Inhulets in two experimental districts. District № 1 was located on the distance 1 kilometer from the overburden dump, which corresponds to the industrial zone. District № 2 was situated on the distance 3 kilometers from the overburden dump, which corresponds to the settlements zone.

Sanitary-chemical investigation of water samples included the following laboratory research: dry residue, total hardness, iron, chloride, sulphate, magnesium, ammonium, calcium, nitrites and nitrates, pH of water (n=132). Sanitary-chemical research of the sediments from artificial reservoirs near the settlements Chervone, Kalinino, Chabanovo, Zaporozhets in Dnipropetrovsk region was carried out (n=123). Research of biological objects – plants and aquatic biota was conducted on the limited number of indicators – content of some heavy metals (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) (n=112). Research of wild plants samples, taken from the residential areas and areas bordering with artificial ponds, was carried out to the contents of heavy metals (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) (n=135). Sanitary-microbiological and parasitological indicators of 1 – 3 years old waste water sludge (WWS), having been taken from aeration stations in Krivoy Rog city (n = 68). Concentrations of the total, mobile, water soluble forms of the given heavy metals (HV) in the 1 – 3 years old WWS, taking from aeration stations in Krivoy Rog city, have been studied (n = 78).

In our research we used local maximum permissible levels of HM in the fish and plant food products, because in Ukraine MPL depends on a background level of chemical pollution in the mining and iron ore processing areas. According to the Ukrainian hygienic standards [11], there is common MPL for different types of sanitary zones: the industrial zone, settlements zone, recreational zone. Therefore, we carried out our experiment in the territory of two sanitary zones. District № 1 was placed on the territory of industrial zone. District № 2 was situated on the territory of settlements zone. We determined the average annual indicators of water quality in the surface water supply source - Karachunovskyi reservoir, which is located in the industrial urbanization zone. The Kryvorozhska zone of urbanization covers city Kryvyi Rih, territory of Karachunovskyi reservoir with SPZ areas; rural areas of Dnipropetrovsk region. The class of water supply source for each of the indicators was determined by ISO 4008: 2007 [12], and water quality from the Karachunovskyi reservoir was analyzed according to Sanitary Rules and Norms № 4630-88 [13]. Among indicators of water quality from Karachunovskyi reservoir were the following: organoleptic - smell, taste and aftertaste, turbidity; total hardness, dry residue, sulphates, chlorides, permanganate oxidation, pH, bichromatic oxidation, soluble oxygen, total organic carbon, chemical content: Mo, As, Ni, Zn, Na–K, Ca, Mg, Fe, Mn, Cu, F, cyanides, calcium phosphate, ammonia nitrogen, nitrite, nitrates, silicic acid, synthetic surfactants, polyphosphates, petroleum products. Totally 33 indicators of water quality were studied. The majority of water quality indicators from Karachunovskyi reservoir were carried out during (2008-2016) years, salt composition of water (content of total hardness, dry residue, sulfates, manganese) was studied.

RESULTS

In the water samples, taken from river Inhulets from the control sites below location of overburden dump, overnormal concentrations of chemical compounds were observed. In the experimental district № 1 we received the following results of laboratory research: dry residue (2.6 maximum permissible level – MPL), total hardness (2.9 MPL), iron (1.8 MPL), chloride (2.3 MPL), sulphate (1.4 MPL), magnesium (3.5 MPL), ammonium (1.1 MPL). In the experimental district № 2 had been shown overnormal concentrations of dry residue (up to 2.1 MPL), total hardness (up to 2.7 MPL), iron (up to 2.1 MPL), chloride (up to 1.7 MPL), sulphate (up to 1.4 MPL), magnesium (3.1 MPL). Concentrations of the calcium, nitrites and nitrates were below hygienic standards. According to the data of laboratory research, pH of water in the both experimental districts was varied (7.4 – 7.9), which corresponds to the hygienic requirements.

Sanitary-chemical research sediments from artificial reservoirs near the settlements Chervone, Kalinino, Chabanovo, Zaporozhets indicated about absence of their anthropogenic chemical contamination by HM. Concentrations of the total and mobile forms of HM in the whole soil samples did not exceed MPL. Sanitary-chemical research of water quality in the stagnant surface waters, having been taken from all rural settlements, included to our scientific work, carried out its compliance with sanitary-hygienic norms. In the local water ponds water samples had excessive total content of inorganic salts (2601.66±602.00) mg/dm^3 (2.6 MPL) and high total hardness (25.16±8.40) mg/dm^3 (3.59 MPL), overnormal concentrations of lead (1.0-2.5 MPL) and cadmium (1.3-7.5 MPL). Results of analyses of wells water located in the rural settlements indicated about its complete unsuitability for drinking purposes. Water from local wells does not correspond to the hygienic requirements: high content of salts (up to 4.97 MPL), total hardness (up to 5.16 MPL), and high turbidity (3.58 MPL). Amount of inorganic salts in some wells was on the level (4971.6±0.07) mg/dm^3, general rigidity (36.16±0.29) mg/dm^3. It was determined high concentrations of toxic metals, such as cadmium (up to 3.7 MPL) and lead (up to 1.53 MPL).

Research of biological objects – plants and aquatic biota was conducted on the limited number of indicators – content of some HM (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe). At the research of aquatic biota – in the fish and amphibians (frogs) biomass was shown, that the concentration of HM (Pb, Cd, Zn, Cu, Cr, Ni, Fe) did not exceed the maximum permissible levels (MPL) for fish products, except content of manganese (table I).

In all samples of fish and amphibians biomass was determined the highest concentrations of manganese and iron, in comparison with other HM. Content total forms of manganese (0.82±0.40) mg/kg exceeded MPL for fish

Table I. Content of heavy metals in the fish and amphibians tissues, taken from stagnant surface water objects near the settlements, located to overburden dump career of Inhulets mining enterprises (n=112)

Form of heavy metals	Concentration, mg/kg (M±m, $X_{0,25}$-$X_{0,75}$)*							
	Pb	Cd	Zn	Mn	Cu	Cr	Ni	Fe
Total	0.46± 0.11 (0.25-0.69)	0.033± 0.008 (0.016-0.052)	1.45± 0.38 (0.66-2.43)	0.82± 0.40 (0.19-1.04)	1.03± 0.41 (0.27-1.43)	0.49± 0.13 (0.24-0.70)	0.26± 0.06 (0.21-0.35)	3.86± 2.13 (0.56-8.26)
Maximum permissible level**	1.0	0.2	40.0	0.76	10.0	-	-	5.0

Note: * -(X0,25-X0,75) – interquartile scope (25 – 75 %); ** - MPL – maximum permissible levels of heavy metals in the fish products.

Table II. Content of heavy metals in the wild plants, taken from stagnant surface water objects near the settlements, located to overburden dump career of Inhulets mining enterprises (n=135)

Form of heavy metals	Concentration, mg/kg (M±m, $X_{0,25}$-$X_{0,75}$)*							
	Pb	Cd	Zn	Mn	Cu	Cr	Ni	Fe
Total	0.21± 0.06 (0.11-0.26)	0.047± 0.007 (0.03-0.06)	<4.0	<50.0	<2.0	<0.5	<4.0	9.03± 0.72 (8.09-9.91)
Maximum permissible level**	0.5	0.1	50.0	-	10.0	-	-	-

Note: * - ($X_{0,25}$-$X_{0,75}$) – interquartile scope (25 – 75 %); ** - MPL – maximum permissible levels of heavy metals in the food products of plant origin.

production in 1.08 times. In some fishes and amphibians specimens content of total forms of iron ranged from (0.56 to 8.26) mg/kg, which corresponded to (0.11 – 1.65) MPL. At the research of wild plants samples, taken from the residential areas and areas bordering with artificial ponds, was found that contents of HM (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) did not exceed MPL for agricultural plants. This indicated about low probability of translocation all these HM and absence of accumulation Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe to the local plants (table II).

By epidemic indicators WWS, keeping in the sludge ponds about 1 year old, were relatively dangerous, and did not contain viable pathogenic microorganisms, but had numerous saprophytic microflora (coliforms and anaerobes) and viable eggs of geohelminths. Sanitary-microbiological indicators of 3 years old WWS corresponded to the uncontaminated soil, they should not contain viable eggs of geohelminths. Given WWS was epidemiology safety (table III).

It have been determined, that average content of the total, mobile and water-soluble forms of HM in the 3 years old WWS did not exceed their threshold concentrations, by the water migration indicator of harm (table IV).

Application WWS with different period of accumulation in order to create artificial soil in all experimental landfills carried out to the increasing saprophytic microorganisms, which should be primary factor in formation of the nutrient humic substances. While applying WWS with 1.5 years of exposition in the experimental plots at the concentration (15 kg/m^2) was observed significant increase amount of mesophilic aerobic and facultative anaerobic microorganisms (MAFAM) from 35000 to 309000 CFU in 1 gram of soil. Average content of MAFAM in all experimental plots was on the level (1.85±0.29)·10^5 CFU in 1 gram of soil ($p<0.01$). The same trend was observed in the experimental soils with (30 kg/m^2) of WWS. Quantity of MAFAM colonies also increased from 31400 to 394000 CFU in 1 gram of soil. Average content of MAFAM in all experimental plots was (2.94±0.26) ·10^5 CFU in 1 g of absolutely dry soil. At the research titre of sanitary-indicative microorganisms have been shown «clean» sanitary condition of soil by coli-titre after 1.5 years and of longer term of WWS exposition. Titre Clostridium perfringens in all experimental samples of artificial soil was (0.1 and > 0.1), which corresponds to the soil characteristic ("clean").

It was determined, that application 1.5 years old WWS at the amount (15 kg/m^2) in the experimental plots did not carried out to the increasing total forms of HM, or their background concentrations, MPL, and clarks. For copper, the total content (5.38±0.29) mg/kg exceeded its background concentration – coefficient of concentration (C_c=2.94). Total content of zinc (20.00±0.31) mg/kg exceeded a background concentration (C_c=3.67). By the total pollution index (Z_c = 1.61), HM contamination of soils from career Inhulets after 6 months accumulation of WWS the soil sanitary state characterized as "permissible". It was found that using WWS on the concentration (30 kg/m^2) in the experimental plots carried out to the significant increase content of total forms of HM: manganese (75.66±0.28) mg/kg, zinc (58.94±0.18) mg/kg and copper (28.45±0.28) mg/kg ($p<0.001$). However, the total pollution index (Z_c = 12.1) corresponds to the "acceptable" level of pollution.

Table III. Sanitary-microbiological and parasitological indicators of 1 – 3 years old waste water sludge, having been taken from aeration stations in Krivoy Rog city (n = 68)

Time of waste water sludge (WWS) accumula-tion in the aeration stations	Total number of saprophytic microorganisms, colony forming units (CFU in 1 gram of WWS)	Titer of anaerobes (Clostridium Perfringens)	Number E. Coli, (CFU in 1 g of soil)	Pathogenic microorganisms all types	Number of the geohelminths eggs (per /100 g)
1 year	$1.5 \cdot 10^7 - 2.2 \cdot 10^7$	0.001-0.0001	890 - 999	should be absent	3-8 *
3 years	$6.0 \cdot 10^3 - 1.5 \cdot 10^4$	0.01	< 100	should be absent	2-5 **

Note: * viable eggs of Fasciola hepatica; ** - non-viable eggs of ascarids (Toxocara canis).

Table IV. Average contents of heavy metals in the 3 years old waste water sludge, having been taken from aeration stations in Krivoy Rog city (n = 78)

Form of heavy metals (HM)	Concentration of HM (mg/kg, limits of variation/mean)*						
	Pb	Cd	Zn	Mn	Cu	Cr	Ni
Total	1.2-106.0 20.0	0.1-4.6 0.2	18.0-259.2 198.1	60.0-232.0 182.3	24.0-165.0 48.9	8.0-33.4 17.6	2.0-73.1 23.5
Mobile	< 0.1	< 0.1	55.1-132.7 77.6	34.0-90.3 55.4	3.2-57.4 12.9	<0.1	0.1-8.9 2.6
Water soluble	< 0.1	< 0.1	30.8-45.9 36.6	10.4-58.7 39.6	0.8-17.4 4.1	<0.1	<0.1
MPL_{total}, (mg/kg)	32.0 (260.0)*	1.5 (1.5)	-	1500.0 (1500)	-	80.0	-
$MPL_{mobile\ form}$, (mg/kg)	-	-	23.0 (200.0)	-	3.0 (72.0)	6.0	4.0 (14.0)
Background soil $_{total,}$ (mg/kg)	18.0	0.09	63.0	612.0	22.0	78.0	25.0

Note: * - in the brackets – threshold concentrations of HM in the soil, estimated by water migration indicator of harm.

Table V. Suitability of WWS for landscape reclamation of the anthropogenic contaminated territories

Degree of validity WWS for landscape reclamation	Indicators of epidemic safety*				Concentration of HM (exceeds of MPL)
	Titre E. Coli	Titre Clostridium Perfringens	Number of geohelminths eggs (in 1 kg of soil, viable)	Pathogenic microorganisms	
Regulated indicators for «suitable» WWS	0.1-1.0 and more	0.01-0.1 and more	should be absent	should be absent	1-10
Results of our research for 1.5 years old WWS accumulation in the soil	0.1-1.0	0.01-0.1 > 1,0	should be absent, except for single non-viable eggs of Toxocara canis	pathogenic enterobacteria, Salmonella, pathogenic Staphylococcus, fungi and yeast should be absent	Pb, Cd, Zn, Ni, Mn < MPL; Cr (3.3 MPL), Cu (1.45 MPL)

Note: * - Titre of thermofils in the experimental plots, taken from Inhulets mining enterprise career should not determine, because a period of survey for thermophilic microorganisms in WWS corresponds from 2-3 to 5-6 months.

In order to assess suitability of WWS for recultivation surface of waste dumps and waste pits we recommended list of epidemic safety indicators and their chemical composition, which are distributed according to such criteria: "suitable", "conditionally suitable" in combination with natural soils or inert rocks, "not suitable". Comparative assessment suitability of WWS carried out at a wastewater treatment plant in Krivoy Rog for landscape reclamation secondary ecosystems was recommended by the "Criteria of epidemic safety and toxicological hazard of WWS" (table V).

For suitable conditions of the soil formation on a surface of overburden dump with optimal ratio of nitrogen, phosphorus and potassium (N:P:K) we proposed intake of WWS on a working dose (300 kg/ha by nitrogen amount) with 70% of humidity and 1.5 year of accumulation in the soil. Based on an average amount of nitrogen in the old WWS (4.5 %), taken from wastewater treatment plant in Krivoy Rog, we recommended maximum amount of WWS (66.7 – 70.0 ton/ha).

In the water from Karachunovskyi reservoir total hardness increasing, according to the levels of average annual indicators:

from 6.76±0.40 mg/dm^3 in 2008-2016 years to 10.28±0.44 mg/dm^3 in 2002-2012 years. During 2008-2016 years in summer period, according to the level of total hardness water from the reservoir concerned to the 3rd class of surface water sources, according to ISO 4008:2007 "satisfactory, acceptable water quality". Dry residue for 2008-2016 years did not exceed the established hygienic standard (1000 mg/m^3), but water from this reservoir belonged to the 3rd class, according to the classification of surface water ISO 4008:2007 [12]. The sulphate content of water from this reservoir was classified as 4 class of hazard for the period of observation 2008-2016 years. By to the content of chlorides was observed dynamics of reduction on 1.34 times: from (139.58±2.49) to (104.33±1.80) mg/dm^3. Water quality belonged to the 3rd class (101-250 mg/dm^3). According to the level of average index 0.262±0.013 mgN/dm^3, ammonium nitrogen corresponded to the 2nd class of quality 0.10 – 0.30 mgN/dm^3. Nitrite nitrogen did not exceed MPC (3.3 mgN/dm^3) for all period of observation. Water belonged to the 3rd class of quality. It should be noted that nitrate nitrogen content showed a negative trend during 2008-2016 years, but concentrations of these compounds did not exceed MPC (45 mgN/dm^3).

DISCUSSION

Results of the study of environmental objects (surface and groundwater, bottom sediments, wild plants, fish and amphibians) in the settlement zone of Dnipropetrovsk region, adjacent to the territory of the worked career, revealed excessive salinization of ponds and mine wells and excess of toxic HM, namely cadmium and lead, which may be a sign of human-made impact on the quality of a long-term waste storage facilities and mine drainage.

Water of mine wells located in the rural settlements (Chervone, Kalinino, Gomelske, Zaporozhets, Chabanovo) is completely unsuitable for drinking purposes due to the excessive content of inorganic salts (4971.6±0.07) mg / dm^3 and increased total stiffness (36.16±0.29) mg eq / dm^3, respectively (4.97 and 5.16) MPC.

It was found that in the body of fish and amphibians (frogs) the content of gross forms of HM (Pb, Cd, Zn, Cu, Cr, Ni, Fe) did not exceed MPL for fish products, except manganese (0.82±0.40) mg/kg and iron (3.86 ± 2.13) mg /kg, concentrations of which exceeded MPC for fish products: for manganese (up to 1.08 MPC) and iron (up to 1.65 MPC). It was found that in the plants - wild grasses in the settlements bordering on ponds, content of gross forms of HM (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) did not exceed MPL for agricultural plant products, which testified to the low probability of mass transfer of these HM according to the translocation indicator of harmfulness and absence a danger of accumulation of Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe in the phytomass of wild grasses.

An innovative technology of using PMWW for the formation of secondary ecosystems, developed and applied by us in the territory of the former career, has many advantages over traditional methods of application of PMWW. Data from the literature and our own research have shown that the current technologies for the use of PMWW are accompanied by pollution of the environment with chemicals and biological substances.

Thus, at the traditional method of using PMWW as organo-mineral fertilizer, there is a risk of contamination agricultural soils by HM, which transfer to the soil from PMWW and pathogens of infectious diseases and geohelminths. Under such conditions, use of PMWW as organic fertilizers poses a risk of contamination fertile soils by HM and inclusion of the latter in food chains, and, as a consequence, transfer into the human body.

Our innovative technology for inclusion of organic matter in the natural cycle is achieved by diluting PMWW with inert materials: natural soils or inert overburden rocks of spent careers. Innovative technology of using PMWW is recommended by us for the formation of human-made landscapes of spent careers will avoid environmental problems associated with epidemiological, toxicological and genotoxic safety of the environment, and prevent the migration of exogenous chemicals to the human body through ecological chains.

CONCLUSIONS

On the basis of Krivoy Rog iron mining ore deposit companies (Ukraine) the complex field studies focused on the fast development of secondary landscapes in the surface of dumps after iron mining were carried out. Overnormal concentrations of salt had been found in water samples, taken from the river Inhulets in a zone of influence breed (2.1 MPL), sulfates and carbonates (2.7 MPL), iron (2.1 MPL), chloride (1.7 MPL), magnesium (3.1 MPL). In the wells from nearest villages water is not suitable for drinking purposes and contains total sum of salts – 4.97 MPL, sulfates and carbonates – 5.16 MPL, cadmium – 3.7 MPL, lead – 1.53 MPL. Thus, the toxic heavy metals concentrations (Pb, Cd, Zn, Mn, Cu, Cr, Ni, Fe) in the fish and amphibians, as well as herbaceous plants in these areas did not exceed the permissible levels.

Use of clearing facilities sludge aged from 1.5 years old and of longer in the amount 15 kg/m^2 did not lead to increased concentration of heavy metals in the top layer of dumps. Total pollution of the soil within six months after application of sludge correspond to the "permissible" level (Z_c =1.61). It was found that water in Karachunovskyi reservoir is not conditioned by salt composition and belongs to the 3-4 class of water supply sources. It has a high content of total hardness, dry residue, sulfates, chlorides for a long time of observation 2008-2016 years, which is explained by the systematic discharge of highly mineralized mine waters from mining enterprises in the city Kryvyi Rih, pollution of the Ingulets and Saksagan rivers, and subsequent pollution water of the reservoir. Unfavorable tendency to self-cleaning water of the reservoir, by the indicators of nitrifying activity during 2008-2016 years was shown.

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Research work was carried out within a framework on the cathedral theme of the research work: "Scientific substantiation ecological and hygienic measures to prevent the negative influence of antropogenic factors on the environment and state of the population health", state registration number 0108U011276 (implementation period 2014-2018 years).

ORCID and contributionship:
Luibov V. Hryhorenko: 0000-0002-9517-5975 [C, D, F]
Svitlana Yu. Yehorova: 0000-0002-2456-4324 [A, B, E]

CORRESPONDING AUTHOR
Luibov V. Hryhorenko
Dnipropetrovsk Medical Academy Ministry of Health of Ukraine
9 Volodymyra Vernadskogo St., 49044 Dnipro, Ukraine
tel: +380680091847
e-mail: hryhorenkoluibov@ukr.net

Received: 10.11.2019
Accepted: 25.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

COMPLEX TREATMENT THE PATIENTS WITH PSORIASIS AND CONCOMITANT ACTIVATED HERPES VIRUS INFECTION, TYPES 1, 2

DOI: 10.36740/WLek202009213

Ulyana V. Fedorova, Orysya O. Syzon, Marianna O. Dashko, Iryna Ya. Voznyak
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

The aim: is to increase effectiveness and assess safety of the antiviral therapy in complex treatment of patients with psoriasis with activated chronic herpes virus infection of types 1 and 2.

Matherials and methods: 120 patients and 25 practically healthy persons were examined.

Results: It has been studied an effect of antiviral therapy on the background of basic therapy in patients with P+HSV 1,2: the percentage of HSV 1,2 DNA detection after the use of acyclovir and/or inosine pranobex was decreased in saliva from 22.0±3.43 % to 6.7±1.32 % ($p<0.01$) and in epithelium – from 33.3±4.23 % to 6.7±1.8 % ($p<0.01$); The use of antiviral therapy has showed a decrease in the expression of miR 155 molecules from 126.3 ±10.5 U/6 to 62.4±5.48 U/6 ($p<0.05$), an increase in the number of T-regulatory lymphocytes from 6.8±1.25% to 9.1±1.41% ($p=0.0503$); a decrease of IFN-α level in saliva from10.1±1.84 ng/ml to 8.2±1.27 ng/ml ($p1=0.0398$); in the serum IL-23 level was significantly decreased from14.9±2.11 pg/ml to 8.8±2.03 pg/ml ($p<0.05$) and TGF-β synthesis was increased from 3.9±1.23 pg/ml to 9.3±2.21 pg/ml ($p<0.01$).

Conclusions: An improved method of treatment and evaluation of its clinical and immunological effectiveness based on an integral criterion was suggested as a result of conducted antiviral therapy amid basic therapy in patients with psoriasis with activated HSV-1 and HSV-2.

KEY WORDS: psoriasis, herpes simplex viruses, type 1 (HSV-1) and type 2, miR155, miR146a, antiviral therapy

Wiad Lek. 2020;73(9 p. II):1968-1972

INTRODUCTION

Nowadays, psoriasis (P) continues to be a common systemic pathology, both in adults (up to 10%) and children (up to 4%). It is often resistant to standard therapy, which has a negative impact on the psychological and emotional status of patients, reduces their ability to work and determines a relevant medical and social problem [1,2,3]. It is established that psoriasis is often associated with many infections, especially viral ones, which can actively influence the pathogenesis and clinical course of dermatosis and determine the effectiveness of treatment [4,5].

Herpes simplex viruses, type 1 (HSV-1) and type 2 (HSV-2), hold a special place among immunotropic opportunistic viruses. Their prevalence is particularly significant in the population: labial - from 67% to 92% and genital - from 25% to 64% [5,6]. Nowadays, the consequences of the activation of chronic HSV-1 and HSV-2 infection, especially in the immunocompromised cohort of the population (up to 20%) under the conditions of its activation, are not studied fully [6,7]. Psoriasis belongs to this group and is the basis of immune dysregulation, in which HSV-1 and HSV-2 infection can actively influence the course of the disease and determine effectiveness of its treatment.

Considering a powerful innovative development of both diagnostic and therapeutic biological technologies, the immunopathogenetic aspects of psoriasis with scientific and practical importance are studied actively [8,9,10]. Existing researches focused on these issues are often controversial [11]. An urgent task of modern dermatology is early detection of activation of HSV-1 and HSV-2 infection in patients with psoriasis and its relations with the clinical course of the disease, as well as establishment of criteria for assessing the levels of immunoregulatory disorders, which substantiates feasibility of antiviral drugs use in complex dermatosis therapy [12,13].

Thus, there is no structured complex and differentiated approach to the therapeutic tactics for managing patients with psoriasis with concomitant HSV-1 and HSV-2 infection. It confirms the feasibility of further study of molecular genetic and immunological mechanisms of disease development in order to develop effective therapeutic and prophylactic interventions for patients.

THE AIM

The aim of the study is to increase effectiveness and assess safety of the antiviral therapy in complex treatment of patients with psoriasis with activated chronic herpes virus infection of types 1 and 2, taking into account molecular genetic and immunological mechanisms of development of these diseases.

MATHERIALS AND METHODS

145 patients were examined using general clinical, general laboratory, biochemical, molecular genetics, immuno-

logical and instrumental methods: 120 patients and 25 practically healthy persons. The following groups were identified: 25 healthy persons (1); 38 patients with P (2); 37 patients with activated HSV 1,2 (3); 45 patients with P and activated HSV 1,2 (P+HSV 1,2) – the main group (4). To compare the effectiveness of the recommended treatment regimens, the patients of the main group were divided into 4 subgroups, taking into account the severity of HSV 1,2 and the use of different antiviral therapy during 3 months: 12 patient (4A) – the use of basic therapy only (order of the Ministry of Healthcare of Ukraine No752 of 20/11/2015); 10 patients with mild P (4B) – antiviral treatment of inosine pranobex (IP) in dose 50 mg/kg/day with basic therapy; 13 patients with moderate and severe P (4C) – the use of acyclovir (AC) with basic therapy in dose 1000 mg/day and IP in dose 50 mg/kg/day;10 patients with moderate and severe P (4D) – the use of AC in dose 1000 mg on the background of the basic therapy.

The clinical evaluation of patients has been performed based on the complaints, general examination, the Dermatology Life Quality Indexes for patients (DLQI) and the Psoriasis Area Severity Index (PASI) in psoriasis. To detect DNA of HSV 1,2 and miR molecules, the molecular-genetic method of polymerase chain reaction was used; in biological media, the level of cytokines, IgM and G to HSV1,2 was measured by enzyme immunoassay, phenotyping of lymphocytes and their activation markers – by flow cytometry method. Statistically obtained results were processed using a licensed program «Statistica 6.0».

RESULTS AND DISCUSSION

Psoriasis is often associated with many infections, especially viral ones (HSV1,2), which can actively influence the pathogenesis and clinical course of dermatosis and determine the effectiveness of treatment [4,5,6,7].

In contrast to patients with P, in patients with P+HSV1,2, the lesions of the body upper part were more often observed: scalp – 71.2 % vs 44.7 % ($p<0.05$), face – 24.4 % vs 7.9 % ($p<0.05$) and upper extremities – 43.3 % vs 36.8 % ($p<0.05$). Common P was found in the majority (80.0%) of patients with P+HSV 1,2 compared to the group of patients with P alone (65.8%; $p<0.05$), where the diffuse type of disease was predominated (34.2 %; $p<0.05$). The typical course of the disease was observed in all patients with P in contrast to the patients with P+HSV 1,2 (71,1 %; $p<0.05$), in whom the exudative P was found – 17.8 % and Barber's limited pustular P – 11.1 % cases. It has been found that in patients with P+HSV 1,2, there was dominated plaque P with mixed (82.2 %; $p<0.01$), guttate with papules arranged in a ring-like configuration (65.6 %; $p<0.05$), expressed (51.1 %; $p<0.05$) and sharply expressed (28.9 %) infiltration of rashes. Instead, in patients with only P, there was dominated the winter (81.6 %; $p<0.01$) type of disease with large plaque, diffuse plaque with a garland-like arrangement of rashes (48.2 %; $p<0.05$), moderate (34.2 %) and expressed degree of psoriatic plaques infiltration (57.8 % patients). In patients with P, there was observed a moderately recurrent process (94.7±3.43 %; $p<0.01$) of moderate severity (62.8±3.04 %; $p>0.05$) in the progressive stage (63.2±4.62 %; $p<0.05$) of disease compared to the main group of patients. At the same time, in patients with P+HSV 1,2 on the background of the dominance of disease moderate severity dominance, there have also been found the severe (31.1±2.74 %; $p<0.05$) and very severe forms of P (6.7±2.34 %; $p<0.05$), mainly in the stationary stage (84.4±5.41 %; $p<0.05$) with a frequently recurrent (73.3±4.26 %; $p<0.05$) course and the tendency to move into a continuously recurrent process. The nature of the psoriatic process was in direct expressed correlation dependence on the detection of viral load and the duration of the last disease exacerbation ($r=+0.6$ and $r=+0.7$, respectively). The frequency of relapses per year and the course of the last psoriasis exacerbation had a direct impact on the nature of the relapse.

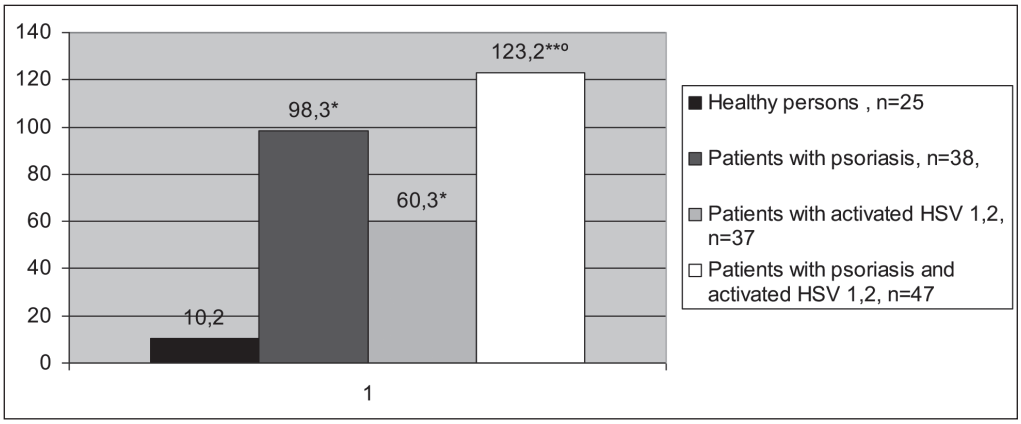
In patients with P+HSV 1,2, index PASI was 20.2±1.46 vs 12.3±1.75 – in patients with P ($p<0.05$). The analysis of the questionnaire for patients with HSV 1,2 has showed an expressed effect of the disease on the quality of life in 28 (62.2 %) patients (DLQI = 27.3±1.7 points), compared to the patients with the only P in 18 (47.3%; $p<0.05$) patients.

We examined 37 patients with activated HSV 1,2 to compare the clinical course of P+HSV 1,2. In patients with P+HSV 1,2, compared to patients with only activated HSV 1,2, there has been dominated the localization of psoriatic rashes often with a wet component, in the genital and intergluteal areas but with less crust formation (70.0±2.62 % vs 6.7±1.07 %; $p<0.01$), higher frequency of crack formation (45.5±3.32 % vs 61.1±4.29 %; $p<0.05$) and more – 2-5 relapses during the year (67.6±8.06 % vs 35.5±4.65 %; $p<0.05$).

The results of the molecular-genetic studies in different biological media have showed that DNA of HSV 1,2 was not detected in patients with P and healthy persons. In patients with activated HSV 1,2, there has been found DNA of Herpes simplex virus infection in the blood – 8.3±2.34 %, in saliva – 12.5±3.28 %, in the epithelium – 29.2±4.54 % cases. In patients with P+HSV 1,2, there have been diagnosed the slightly higher parameters of this virus in biological media, compared to the previous group: in saliva – 20.0±3.89 % ($p<0.05$), epithelium – 33.3±4.38 % ($p<0.05$) patients, and in the blood – not found ($p<0.001$). In patients with P+HSV 1,2, compared to the patients with activated HSV 1,2, specific DNA was more often found in saliva – 1.7 times and in epithelium – 2.3 times.

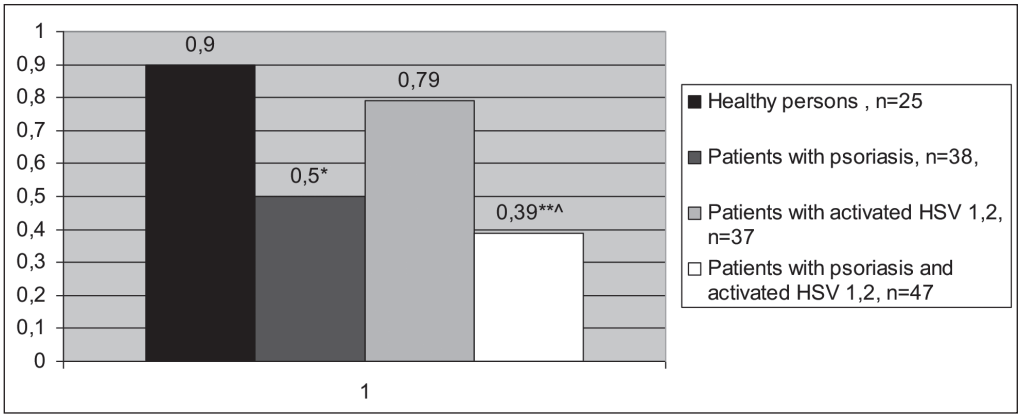
We observed an increased level of IgM to HSV 1,2 in patients with activated HSV 1,2 (1.1±0.08 g/l; $p<0.05$) and in patients with P+HSV 1,2 (0.6±0.09 g/l; $p<0.05$), compared to the healthy persons and patients with only P (0.3±0.48 g/l; $p<0.05$). In patients with activated HSV 1,2 and patients with P+HSV 1,2, synthesis of specific IgG was significantly increased (6.9±2.33 g/l; $p<0.001$ and 3.61±1.02 g/l; $p<0.01$), compared to the healthy persons and patients with only P (1.9±0.75 g/l; $p<0.05$).

Increased expression of miR 155 has been detected in patients with P (98.3±9.92 U/6; $p<0.05$), activated HSV 1,2



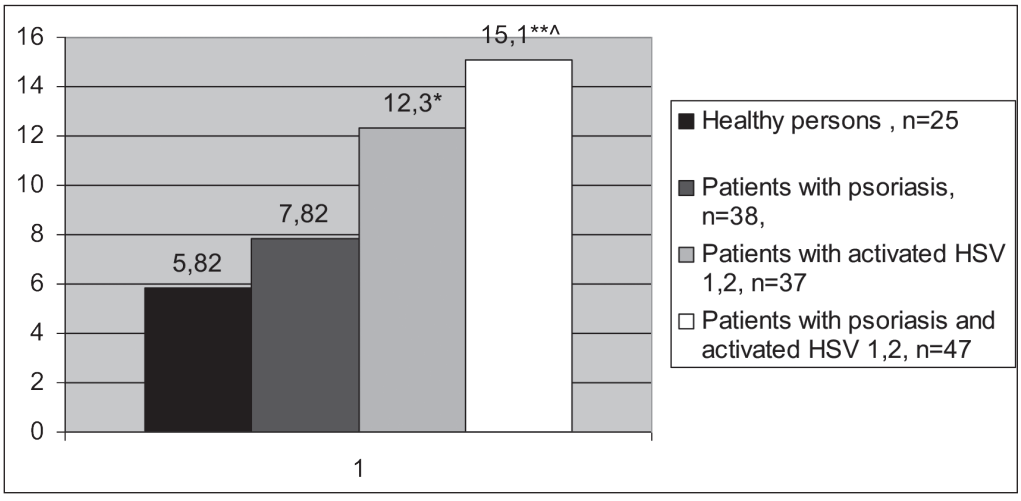
Note: * - value of statistical difference with "healthy" group; ^ - value of statistical difference with the group "P"; ° - value of statistical difference with "HSV-1 and HSV-2" group

Figure 1. The expression level of miR 155 molecules (U/6) in blood serum of the studied groups of patients and apparently healthy persons



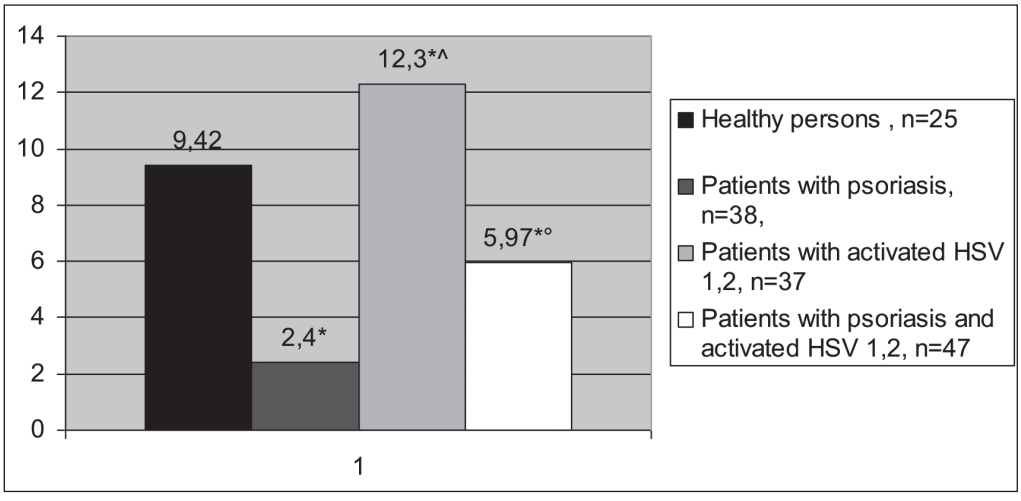
Note: * - value of statistical difference with "healthy" group; ^ - value of statistical difference with the group "P"; ° - value of statistical difference with "HSV-1 and HSV-2" group

Figure 2. The expression level of miR 146a (U/6) molecules in blood serum of the studied groups of patients and apparently healthy persons



Note: * - value of statistical difference with "healthy" group; ^ - value of statistical difference with the group "P"; ° - value of statistical difference with "HSV-1 AND HSV-2" group

Figure 3. Levels of interleukin-23 (ng/ml) in blood serum of the studied groups of patients and apparently healthy persons



Note: * - value of statistical difference with "healthy" group; ^ - value of statistical difference with the group "P"; ° - value of statistical difference with "HSV-1 AND HSV-2" group

Figure 4. Levels of transforming growth factor-β (ng/ml) in blood serum of the studied groups of patients and apparently healthy persons

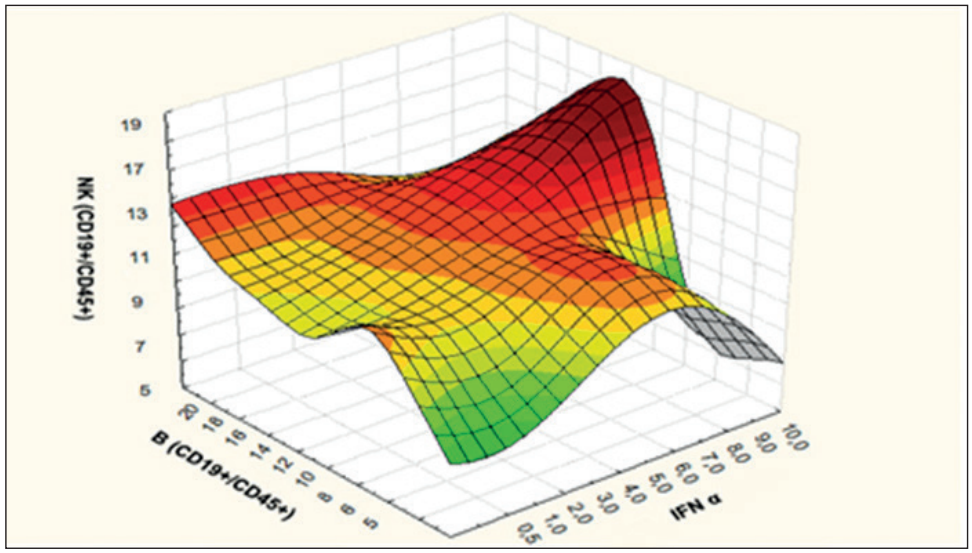


Figure 5. Multivariate analysis of relations between B-lymphocytes, NK cells, and level of interferon-α synthesis in blood serum of patients with psoriasis-activated HSV-1 and HSV-2 after antiviral and basic therapy

(60.3±7.32 U/6; p<0.05), especially P+HSV 1,2 (123.2±8.42 U/6; p<0.01), compared to the healthy persons. At the same time, the synthesis of miR 146a was significantly reduced in patients with P+HSV 1,2, compared to the healthy persons (0.4±0,06 U/6; p<0.01) and patients with activated HSV 1,2 (0.8±0.08 U/6; p<0.05). The expression level of miR 155 molecules was higher 2.04 times and miR 146a molecules lower 1.80 times (p<0.05) in patients with P+HSV 1,2, compared to the group of patients with P.

It has been studied an effect of antiviral therapy on the background of basic therapy in patients with P+HSV 1,2: the percentage of HSV 1,2 DNA detection after the use of acyclovir and/or inosine pranobex was decreased in saliva from 22.0±3.43 % to 6.7±1.32 % (p<0.01) and in epithelium – from 33.3±4.23 % to 6.7±1.8 % (p<0.01); the Ig M level was decreased in subgroups of patients (4B+4C) with inosine pranobex or combination with acyclovir (p<0.05). The use of antiviral drugs has reduced the number of patients with P+HSV 1,2 with replication of Herpes simplex virus infection in saliva – 4.9 times, in the epithelium – 3.3 times. IgG level was increased after basic treatment (4A) to 4.8±1.32 g/l (p<0.05) and in patients after acyclovir with basic treatment (4D) to 3.5±0.92 g/l (p<0.05) that can indicate further periodic replication of HSV 1,2 in these subgroups. In 4B and 4C subgroups, the use of antiviral therapy has showed a decrease in the expression of miR 155 molecules from 126.3 ±10.5 U/6 to 62.4±5.48 U/6 (p<0.05), while increasing the expression of miR 146a from 0.36±0.05 U/6 to 0.7±0.08 U/6 (p<0.05) that also distinguished these patients from subgroup 4A (p<0.05). It has been found a direct correlation between lymphocyte counts and miR 155 molecule expression in the blood of patients treated with inosine pranobex and/or acyclovir (r=0.46; p<0.05). Various epigenetic effects alter the synthesis of miR molecules in the study groups, which is reflected in the activity of proinflammatory miR 155 and inhibitory miR 146a (Fig. 1-2).

By evaluating the features of blood lymphocytes phenotyping in the investigated patients, we have found: an increase in the number of T-helper cells (44.2±2.47%; p<0.01) and a decrease of regulatory T-lymphocytes (4.2±1.08 %; p<0.05) in patients with P compared to healthy persons. The same relationships were observed in patients with P+HSV 1,2 (48.9±3.99 %; p<0.01 – 6.9±1.30%; p<0.05), respectively, compared to healthy persons but still this group had a higher number of regulatory T-lymphocytes, compared to patients with only P (p<0.05).

In patients receiving combined antiviral therapy, an increase in the number of T-regulatory lymphocytes from 6.8±1.25% to 9.1±1.41% (p=0.0503) has been found after treatment (4B+4C), in contrast to patients receiving basic therapy (4A), where was observed a decrease from 8.3±1.12 % to 5.2±1.44 % (p=0.0496). After combined therapy in patients with P+HSV 1,2, the following relationships of average strength we have revealed: a direct relationship between B- lymphocytes and T-regulatory cells (r=0.41; p<0.05), inverse – between T- helper cells and T- cytotoxic lymphocytes (r=-051; p<0.05), multifactorial – between T-, B- lymphocytes and activated T-lymphocyte population, confirming the balance of cellular immunological processes regulation in treated patients using of antiviral drugs.

It has been performed the comparison on activity of IFN-α, IL-23 and TGF-β synthesis in different biological fluids in the studied groups of patients. In patients with P, the level of IFN-α synthesis – an important antiviral cytokine was lower than in patients with activated HSV 1,2 (p=0.0168) and in patients with P+HSV 1,2 (p=0.0276). In patients with P+HSV 1,2, it has been found an increase of IFN-α synthesis in serum 3.5 times, compared to healthy persons and 2.8 times, compared to the patients with P. A key pro-inflammatory cytokine associated with the development of autoimmune skin inflammation is IL-23, whose level in patients with P was 12.3±2.81 ng/ml (p<0.01) and in patients with P+HSV 1,2 – 15.1±3.21 ng/ml (p<0.001), compared to the practically healthy persons (5.82±2.73 ng/ml). It is important to note that patients with P+HSV 1,2 had the most powerful synthesis of IL-23 and its level was significantly different from the group of patients with activated HSV 1,2 – 15.1±3.21 ng/ml vs 7.82±2.01 ng/ml (p<0.05). In patients with P+HSV 1,2, we observed an increase of IL-23 levels 2.6 times, compared to healthy persons, and 1.9 times, compared to the

patients with activated HSV 1,2. A significant role in the regulation of the immune response belongs to TGF-β. In patients with P and P+HSV 1,2, the comparison of its synthesis has showed the differences from the synthesis in healthy persons ($p<0.01$ and $p<0.05$), respectively, with no significant difference between them. In patients with activated HSV 1,2, the synthesis of this cytokine was activated – 12.3±3.48 ng/ml but no significance, compared to healthy persons. In patients with P+HSV 1,2, we observed a decrease of serum TGF-β synthesis – 1.9 times, compared to healthy persons, and 2.1 times, compared to the patients with activated HSV 1,2 (Fig. 3-4).

In subgroups of patients with P+HSV 1,2 after combined antiviral treatment (4B+4C), we observed a decrease of IFN-α level in saliva from10.1±1.84 ng/ml to 8.2±1.27 ng/ml ($p1=0.0398$) but its blood level was not significantly changed, although it was higher than in subgroup (4D) receiving basic therapy and acyclovir ($p=0.0437$). In the serum of these patients after complex treatment, IL-23 level was significantly decreased from14.9±2.11 pg/ml to 8.8±2.03 pg/ml ($p<0.05$) in contrast to the 4D ($p<0.05$) and 4A ($p<0.05$) subgroups and TGF-β synthesis was increased from 3.9±1.23 pg/ml to 9.3±2.21 pg/ml ($p<0.01$), compared to the same subgroups. In patients from 4B + 4C subgroups, these therapeutic tactics has showed the restoration of the relationships between the number of B-lymphocytes, NK-cells and IFN-α synthesis in the blood serum (Fig.5).

It provides the use of Inosine pranobex and/or Acyclovir amid a standard therapy for 90 days depending on the severity of HSV-1 and HSV-2, which contributes to the improvement of clinical and immunological effectiveness and safety of treatment of such patients compared with patients receiving only basic therapy: "marked improvement" 39.1±3.4 vs. 0%, "improvement" - 56.5±3.15 vs. 58.3±5.93%, "no improvement" - 4.35±0.08% vs. 41.7±3.15%.

CONCLUSIONS

An improved method of treatment and evaluation of its clinical and immunological effectiveness based on an integral criterion was suggested as a result of conducted antiviral therapy amid basic therapy in patients with psoriasis with activated HSV-1 and HSV-2.

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Scietific research work

State registration number: 0116U004506
Cipher: IH. 25. 01. 0001. 16
Clinical and experimental justification of monitoring of diagnostics and standardized methods for treatment of metabolic disorders of internal organs and skin and their complications.

ORCID and contributionship:

Ulyana V. Fedorova: 0000-0002-7148-3754 A, B, C, D, E, F
Orysya O. Syzon: 0000-0002-7011-2521 A, D, E, F
Marianna O. Dashko: 0000-0001-6441-5326 C, D, E, F
Iryna Ya Voznyak: 0000-0001-7735-4358 E, F

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Marianna O. Dashko
Danylo Halytsky Lviv National Medical University
1 Konovalets str., 79014 Lviv, Ukraine
tel: +380677691977; +380504131489
e-mail: mariannadashko@gmail.com

Received: 23.04.2020
Accepted: 17.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

RESULTS OF ACUTE PURULENT CHOLANGITIS TREATMENT WITH GENETIC ENGINEERING ANALOGUE OF DORNAZE-ALPHA NATURAL ENZYME

DOI: 10.36740/WLek202009214

Mariya I. Pokidko, Igor M. Vovchuk, Oleh A. Yarmak
NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: to evaluate the effectiveness of the proposed method of surgical treatment of patients with acute purulent cholangitis.

Materials and methods: The research is based on the analysis of the treatment results in 104 patients with acute purulent cholangitis. The volume of surgical interventions on the biliary tract in patients was as follows: endoscopic papillosphincterotomy (EPST) + naso-biliary drainage; EPST + laparoscopic cholecystectomy; cholecystectomy + choledocholithotomy + drainage of the common bile duct.

Results: The APACHE-2 scale assessment for patients in the control group was 12,80 ± 1,73, with the SOFA scale - 4,32 ± 0,31 points. Accordingly, the assessment for patients in the main group with the APACHE-2 scale is 11.76 ± 0.81, with the SOFA scale - 4.33 ± 0.79 points. The results obtained in both the control and the main group indicate that the physiological reactions of the organism to the disease, treatment, development of organ dysfunction are reflected in the integrated severity assessment scales.

Conclusion: The performed analysis of clinical and laboratory results of treatment in both groups established the high efficiency of the proposed treatment method in patients with acute purulent cholangitis, which promotes the more rapid medical and social rehabilitation in this category of patients.

KEY WORDS: cholangitis, biliary tract surgical procedures, endoscopic papillotomy

Wiad Lek. 2020;73(9 p. II):1974-1977

INTRODUCTION

According to WHO, acute purulent cholangitis (APC) without surgical intervention leads to lethal consequences in 98.7% of patients. Purulent inflammation of the intrahepatic bile ducts is accompanied by pronounced dystrophic changes in the liver parenchyma. Microscopically, the walls of the duct are infiltrated with leukocytes, the spread of the purulent process to the surrounding tissue (pericholangitis) and formation of the so-called cholangitic abscesses are possible. In case of purulent cholangitis the suppuration and necrosis with perforation leads to the development of biliary or biliary-purulent peritonitis. Healing of purulent ulcerative cholangitis is followed by granulation and epithelization of ulcers with subsequent sclerosis and deformation of the duct [1,2,3,4].

The penetration of microbial bodies from bile into the systemic circulation accompanied by hemodynamic disorders, which in clinical practice manifests itself in the form of acute biliary septic shock. According to the research, biliary sepsis develops in 39.1% of patients with acute cholangitis, moreover, a fulminant course of the disease developement is observed more often [5,6].

Over the past three decades, optimization of the traditional ways of APC treatment has taken place, namely, new surgical techniques have been introduced: laparoscopic cholecystectomy, EPST, transcutaneous transhepatic cholangiostomy. Analyzing data from various sources, surgical manipulations on the biliary tract in patients are accompanied by complications in 8.3-43% of cases and the mortality rate of 6.2 to 28.6% of cases. EPST with nasobiliary drainage is one of the most effective methods of cholangitis treatment, and the percentage of recovery without complications is 83.5%. This method proved to be safe in the category of operated patients over the age of 60 years. The incidence of fatalities is 1.5%. Taking into account the disadvantages of previous treatment methods, we have proposed a new way of optimizing surgical intervention and postoperative correction [7,8,9,10].

Recombinant human DNA-ase (Dornase-alpha) is a genetic engineering analogue of a natural human enzyme that cleaves the extracellular DNA, so the targeted effect of Dornase-α is to effectively degrade the extracellular DNA by hydrolysis, which causes the degradation of the pathological secretion, exhibits anti-inflammatory properties in the form of reduction of edema and hyperemic reactions.

In order to confirm the effectiveness of the gene-engineering variant of the natural enzyme Dornase-alpha in the treatment complex of acute purulent cholangitis, a number of studies were carried out at the Department of Surgery No. 2 clinic, Vinnitsa National Pirogov Memorial Medical University.

THE AIM

The aim is to evaluate the effectiveness of the proposed method of treatment in patients with acute purulent cholangitis.

Table I. Methods of surgical intervention in patients with APC (n = 50)

Type of surgery	Control group (n=50)	Percents
EPST	28	56%
EPST + laparoscopic cholecystectomy	8	16%
cholecystectomy + choledocholithotomy + drainage of the common bile duct	14	28%

Table II. Comparative characteristics of cytolysis and cholestasis syndrome indicators in the control and the main groups of patients (n = 104) (M ± m)

Indicator	Group	1 day	5 day	9 day	12 day	Discharge
Total bilirubin, mkmoll/l	Control group	308,5 ± 18,46*	188,42 ± 13,48*	107,96 ± 6,28	68,8 ± 3,23*	26,18 ± 1,18*
	Main group	289,29 ± 11,01*	191,04 ± 10,07*	90,20 ± 4,23*	53,90 ± 1,94*	18,61 ± 0,58*
Direct bilirubin, mcmol/l	Control group	228,53 ± 14,62*	122,53 ± 10,22*	57,19 ± 3,79*	33,49 ± 2,56*	10,32 ± 0,69*
	Main group	209,54 ± 10,56*	112,62 ± 9,13*	49,03 ± 4,34*	23,06 ± 1,26*	6,52 ± 0,44*
Indirect bilirubin, mcmol/l	Control group	80,01 ± 5,08*	64,8 ± 4,6*	48,45 ± 3,57*	34,0 ± 2,6*	16,26 ± 1,21*
	Main group	80,87 ± 1,58*	74,7 ± 3,09*	53,49 ± 2,14*	30,84 ± 1,94*	12,18 ± 0,61*
ALT, mmol/l	Control group	7,14 ± 0,067*	4,45 ± 0,06*	2,56 ± 0,037*	1,56 ± 0,4*	1,03 ± 0,013*
	Main group	5,06 ± 0,04*	3,68 ± 0,05*	2,31 ± 0,03*	1,38 ± 0,03*	0,63 ± 0,02*
AST, mmol/l	Control group	5,3 ± 0,027*	2,99 ± 0,014*	1,63 ± 0,011*	1,107 ± 0,024*	0,79 ± 0,014*
	Main group	4,89 ± 0,03*	2,07 ± 0,01*	1,28 ± 0,02*	0,99 ± 0,02*	0,51 ± 0,02*

Note. * - for the average parameter value compared with the norm p <0,05

MATERIALS AND METHODS

The research is based on the analysis of the treatment results in 104 patients with acute purulent cholangitis (APC) who were managed in the period from 2010 to 2017 in the surgical clinic of the Department of Surgery №2 of Vinnitsa National Pirogov Memorial Medical University and Vinnytsa center of liver, extrahepatic bile ducts and pancreatic surgery. Clinical studies were carried out in compliance with the basic provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific Medical Research with Human Participation (1964-2000) and the Order of the Ministry of Health of Ukraine No. 281 of November 1, 2000.

The volume of surgical interventions on the biliary tract in patients was as follows: endoscopic papillosphincterotomy (EPST) + naso-biliary drainage; EPST + laparoscopic cholecystectomy; cholecystectomy + choledocholithotomy + drainage of the common bile duct.

The control group consisted of 50 patients with APC. The obtained data were compared with the main group of 54 patients. In the main group of patients, we proposed a new method of treating APC, which comprises the use of Pulmozim (active ingredient - Dornase-alpha) for lavage of the comon bile duct drainage in APC, given that purulent exudate contains a high concentration of extracellular DNA - a viscous polyanion, which accumulates as a result of leukocytes destruction within the inflammatory process. Taking into account the disadvantages of previous treatment methods, we proposed the way to optimize surgical intervention and postoperative correction. The patent of Ukraine No. 8773/ZU/18 for the utility model "A method of treatment of acute purulent cholangitis" was obtained. The method is carried out in the following manner: EPST + nasobiliary drainage is performed. Corrective treatment, carried out by introducing of the Dornase-alpha solution in 0.9% NaCl into the nasobiliary drainage for 5 days (1 time per day) of the postoperative period, together with complex multicomponent intensive care according to the Order of the Ukraine Ministry of Health No. 297 dated 02.04.10. "Standards of medical care for patients with urgent surgical diseases of the abdominal cavity".

An assessment of systemic inflammation was performed according to the recommended criteria of the Chicago Coordinatory Conference on Intensive Care (USA, 1992), according to which the systemic inflammatory response syndrome (SIRS) was determined in the presence of two or more symptoms.

Determination of the severity of the diagnosed APC was based on assessing the patient's condition according to the APACHE 2 and SOFA scales.

RESULTS AND DISCUSSION

Indications for emergency and urgent surgical intervention were: destructive forms of calculous cholecystitis; cholangitis, resistant to conservative therapy; mechanical jaundice; combined destructive inflammatory pathology of extrahepatic bile ducts (destructive cholecystitis, cholangitis and mechanical jaundice); acute blockade of the common bile duct terminal part (Table I). The volume of surgical interventions on the biliary tract in patients was as follows:

- EPST + nasobiliary drainage;
- EPST + laparoscopic cholecystectomy;
- cholecystectomy + choledocholithotomy + drainage of the common bile duct.

Table III. Duration of the hospital stay of patients with acute purulent cholangitis, depending on the treatment metod (n = 104)

Criteria	Control group (n=33)	Main group (n=31)
Duration of the hospital stay	16,87±3,08*	10,0±1,85
Duration of the ICU treatment	3,1±0,42*	1,7±0,32

Note. * - p <0,05, the reliability of differences compared to the main group.

The assessment of patients in the control group according to APACHE-2 - 12,80 ± 1,73, with the SOFA scale - 5,32 ± 0,31 points. Accordingly, the assessment for patients in the main group with the APACHE-2 scale showed 11.76 ± 0.81, with the SOFA scale - 4.33 ± 0.79 points (p < 0,01).

The dynamics of changes in the indicators of the cytolysis and cholestasis syndrome in patients of the control and the main groups during the application of traditional and optimized complex therapy methods was analyzed (Table II).

The analysis of the dynamic changes of the total bilirubin showed that before the first day of treatment the difference between the control (308.5 ± 18.46; 188.42 ± 13.48) and the main (289.29 ± 11.01, 191.04 ± 10.07) group was not determined (p> 0.05). However, since the ninth day of treatment and at the time of its completion, the difference was reliable (p<0.05) between the next indices: (107.96 ± 6, 28; 68.8 ± 3.23; 26.18 ± 1.18) (90.20 ± 4.23; 53.90 ± 1.94; 18.61 ± 0.58).

The study of the dynamics of changes in direct bilirubin in patients from control and main groups showed that the reliable difference in values was not determined. During the first day of treatment (228.53 ± 14.62, 209.54 ± 10.56 (p> 0.05) and during the entire subsequent term until the end of treatment the difference was reliable (122.53 ± 10.22; 57.19 ± 3.79; 33.49 ± 2.56; 10.32 ± 0.69), (112.62 ± 9.13, 49.03 ± 4.34, 23.06 ± 1.26, 6.52 ± 0.44) (p <0.05).

The analysis of the dynamic changes of ALT in patients within control and main groups found that by the ninth day of treatment the reliable difference between the groups was not observed (p> 0.05) (7.14 ± 0.067, 4.45 ± 0.06, 2.56 ± 0,037) (5,06 ± 0,04; 3,68 ± 0,05; 2,31 ± 0,03) (8,15 ± 0,36; 7,18 ± 0,39), but from the twelfth day of treatment and till its completion, the difference was reliable (1.56 ± 0.4; 1.03 ± 0.013) (1.38 ± 0.03; 0.63 ± 0.02) (p <0.05).

When comparing the duration of the hospital stay as well as the duration of ICU treatment in the main and control group the significantly better results were observed in the group with the proposed treatment method (Table III).

The results obtained in both the control and the main groups indicate that the physiological reactions of the organism to the disease, treatment, development of organ dysfunction are reflected in the integrated severity assessment scales. Along with the other indicators, a significant decrease in AST was determined. During the first day, this indicator was stably high (5.3 ± 0.027) (4.89 ± 0.03). On the fifth day after surgery, AST decreased significantly (1.99 ± 0.014) (1.97 ± 0.01). Subsequently, in the main group, the AST level was lower throughout the follow-up period (p <0.05), before discharge it was 0.51 ± 0.02, compared to the rate, observed in the studied patients (0.79 ± 0.014) who were treated using traditional methods.

On the basis of the cytolysis and cholestasis syndromes analysis in patients within control and main groups, the high effectiveness of the proposed treatment method for patients in the experimental group was established in comparison to the traditional methods used in patients of the control group.

CONCLUSIONS

1. The use of low-traumatic miniinvasive technologies for the prevention of postoperative and purulent-necrotic complications in patients of the main group led to a significant improvement in the results of treatment compared to the control group. The comparative estimation of treatment in patients with acute purulent cholangitis showed that the use of the developed method and its inclusion in the program of integrated optimized treatment allowed to reduce the period of inpatient treatment of patients with acute purulent cholangitis by 6.8 days (from 16.87 to 10).
2. The conducted analysis of clinical and laboratory results of treatment of patients in the control and the main groups has established the high efficiency of the proposed treatment method for patients with acute purulent cholangitis, which forms the conditions for more rapid medical and social rehabilitation of this category of patients.

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ORCID and contributionship:
Mariya I. Pokidko: 0000-0002-1640-7230 [A,E,F]
Igor M. Vovchuk: 0000-0002-0613-9383 [B,C]
Oleh A. Yarmak: 0000-0002-4103-7614 [D]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Oleh A. Yarmak
National Pirogov Memorial Medical University
56 Pirogova Vulytsia, 21000 Vinnytsia, Ukraine
tel:+380634604538; +4915257506075
e-mail:yarmakoleg@gmail.com

Received: 27.10.2019
Accepted: 09.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

PARTIAL LAPAROSCOPIC ADRENALECTOMY - ANATOMICAL BASIS AND OPERATION TECHNIQUE

DOI: 10.36740/WLek202009215

Sergiy P. Styopushkin, Viktor P. Chaikovskyi, Volodymyr A. Chernylovskyi, Ruslan V. Sokolenko
DNIPROPETROVSK CITY MULTIFIELD CLINICAL HOSPITAL №4 "DRU", DNIPRO, UKRAINE

ABSTRACT

The aim: To optimize the indications for partial laparoscopic adrenalectomy (PLA), to give a detailed outline of a PLA technique and to provide technical tips to ensure safe and highly-effectiveness, based on the knowledge of adrenal anatomy and blood supply.

Materials and methods: Between January 2010 and September 2018, our department performed 47 adrenal glands surgeries. The operations included 29 total laparoscopic adrenalectomies (TLA), 4 open adrenalectomies (OA) and 14 partial laparoscopic adrenalectomies (PLA).

Results: The histopathological examination of all operated patients detected 9 (19.1%) malignant tumors, including 5 metastatic tumors. Benign tumors includes 24 (63%) adenomas, 8 (21%) pheochromocytomas, 4 (10,5%) cysts and 2 (5,5%) ganglioneuromas. Post-PLA histopathological findings revealed 6 adenomas, 2 pheochromocytomas, 4 cysts and 2 ganglioneuromas.

Conclusions: Keeping in mind anatomical features of adrenal gland blood supply in highly-selected patients, PLA can be performed in a number of patients. 2 mm of a minimal resection margin is enough to preserve a false tumor recurrence. Anatomically grounded PLA is becoming a new standard of benign adrenal gland tumors treatment, providing an opportunity to save more adrenal gland functional tissue and to prevent hipocorticism development in postoperative period.

KEYWORDS: ganglioneuroma, pheochromocytoma, adrenal gland, partial laparoscopic adrenalectomy, adrenal gland adenoma

Wiad Lek. 2020;73(9 p. II):1980-1984

INTRODUCTION

The main goal of this article is to optimize the indications for partial laparoscopic adrenalectomy (PLA), to give a detailed outline of a PLA technique and to provide technical tips to ensure safe and highly-effectiveness, based on the knowledge of adrenal anatomy and blood supply. In this paper, a special focus is placed on the surgical technique of PLA. This operation was standardized and can be performed with good results.

In recent years, total laparoscopic adrenalectomy (TLA) substituted open adrenalectomy (OA) and became a gold standard for treatment of adrenal gland benign tumors.

The latest findings confirm the use of minimally invasive surgery for treatment of adrenal tumors and prove TLA to be an effective and safe method comparable to OA in operation time and complications rate, yet having the potential for shorter hospital stay, lower blood loss and better cosmetic effect.

PLA is a new step of treatment of adrenal tumors. The main advantage of this operation is a preservation of functional tissue of adrenal gland, which reliably helps to avoid hipocorticism. Walz [1] first provided minimal invasive partial adrenalectomy with retroperitoneal approach, and this surgery showed good treatment results and helped to avo rmone-replacement therapy. Janetschek described PLA-experience in patients with aldosterone-productive adenoma [2] and pheochromocytoma [3]. In the case of bilateral hormone-productive tumors (pheochromocytoma, aldosterone- and cortisol-productive adenomas), special emphasis is put on the advantages of this surgery, which makes it possible to preserve a bigger volume of functional tissue and reduce the risks of cortical insufficiency development in the case of contralateral tumor [4]. Knežević N [5] determined operative indications for tumors located predominantly in the adrenal gland margin. In his systematic review, Nagaraja [6] showed a recurrence free rate 8% (95% CI: 0.05e0.12), whereby 85% of operated patients (95% CI: 0.78e0.9) did not require further post-PLA corticosteroid replacement therapy.

At the same time, despite the preservation of adrenal gland tissue or providing adequate steroid therapy, Addison crisis can be detected in 10-35% of patients [4]

Rich blood supply is a necessary condition for optimal adrenal gland functioning. Adrenal gland blood supply (Figure 1) is implemented 20-30 thin arterial branches from right superior adrenal aa. (from inferior phrenic a.), middle adrenal a. (from abdominal aorta) and inferior adrenal a. (from renal a.).

Sinusoid blood capillaries form central vein inflows into inferior vena cava near the right adrenal gland and into the right adrenal gland on the left. Adrenal glands (especially the left one) contain small veins, which flow into portal vein inflows [7].

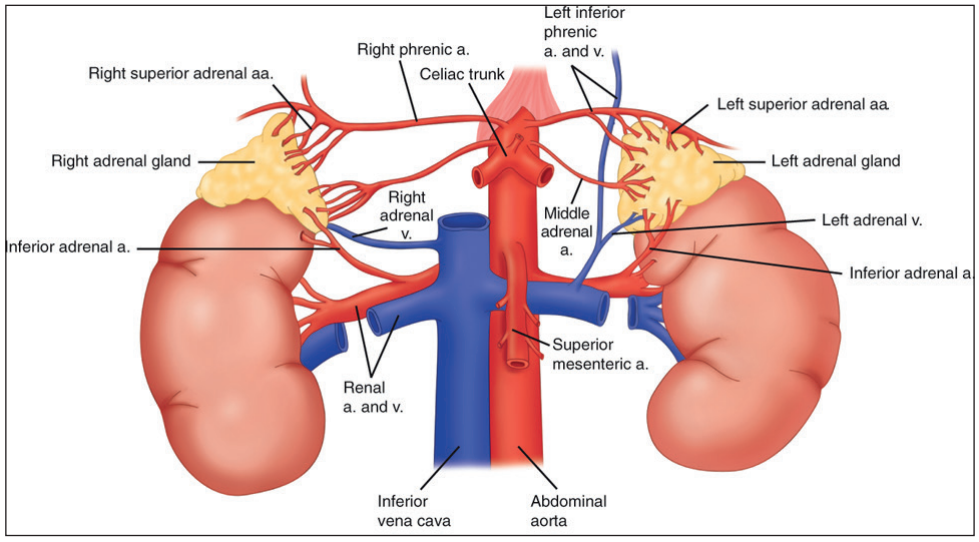

Fig. 1. Adrenal Gland Blood Supply

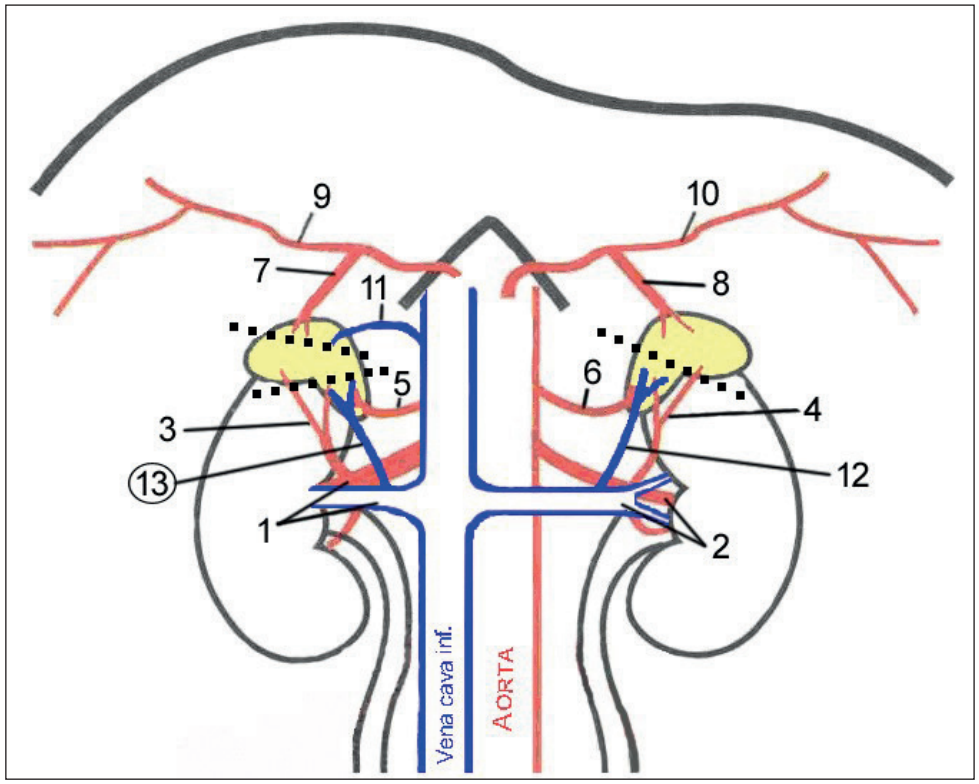

Fig. 2. Partial Adrenalectomy Options. (Signed resection areas/Dotted Lines = Resection Areas). 1-Right renal artery and vena, 2- Left renal artery and vena, 3-Right inferior adrenal artery, 4- Left inferior adrenal artery, 5- Right middle adrenal artery, 6- Left middle adrenal artery, 7- Right superior adrenal artery, 8- Left superior adrenal artery, 9-Right inferior phrenic artery, 10- Left inferior phrenic artery, 11-Right adrenal vena, 12- Left adrenal vena, 13-Accessory right adrenal vena (25% cases).

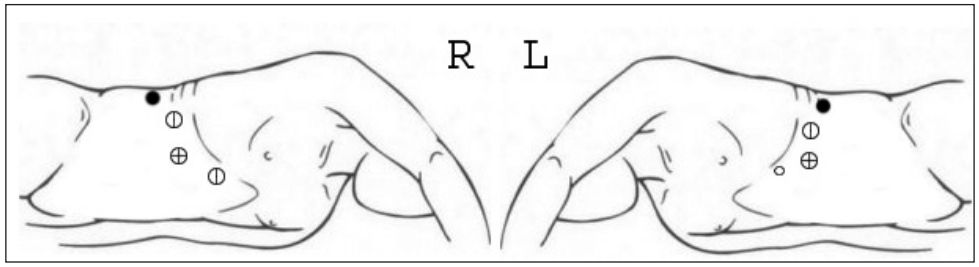

Fig. 3. Trocar placement: ⊕ - Optic (10mm), Ⓡ - 11mm trocar, ○ - 6 mm trocar, ● – additional trocar.

The indications for organ-sparing adrenal gland operations include cystic lesions, benign tumors up to 4 cm., especially hormone-productive tumors (e.g. aldosteronoma, glucocorticoid-, androgen- and estrogen-productive adenomas) and bilateral tumor. To absolute contraindications belong adrenal gland malignant tumors and metastatic tumors. Relative contraindications include extensive benign tumor mass, presence of multifocal tumors and poor blood supply to residual adrenal gland tissue. Sufficient amount of residual tissue is not yet determined. E.K. Diner [8] believes that the preservation of 3-5 mm is enough to achieve good postoperative results.

General contraindications include Cushing's disease (secondary hypercortisolism), severe cardiac pathology, heart failure, uncontrolled coagulopathy etc.

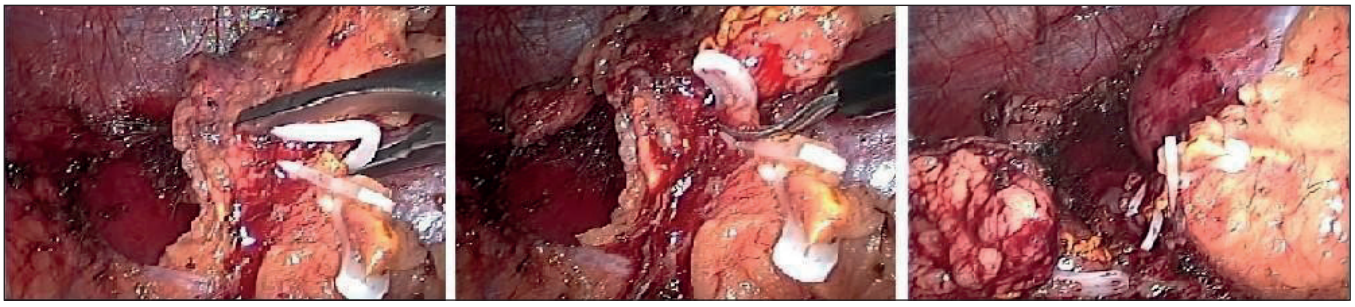

Fig. 4. Resection Margin Clipping with Hem-o-lok Clips.

Table I. Adrenal Gland Tumors: Histological Types.

	PLA(n-14)	TLA (n-33)
Right-sided	6 (43%)	18 (55%)
Left-sided	8 (57%)	15 (45%)
Median age (years)	63	62
Histological type		
Malignant tumors		
Primary adrenal gland tumor (adrenocortical cancer)	-	4 (14%)
Lung cancer metastasis	-	4 (14%)
Uterine carcinoma metastasis	-	1 (3%)
Benign tumors		
Adenoma	6 (43%)	18 (63%)
Pheochromocytoma	2 (14%)	6 (21%)
Cysts	4 (28%)	-
Ganglioneuroma	2 (14%)	-
Hormone-producing tumors	8 (57%)	19 (58%)
Non hormone-producing tumors	6 (43%)	14 (42%)

All patients underwent Abdominal and Retroperitoneal Ultrasound and contrast-enhanced (Tomohexol/Omnipack) Chest, Abdomen and Pelvis CT-scan. An endocrinologist and GP examined patients. Serum level of aldosterone, cortisol, catecholamines and urine metanephrine was measured. To exclude secondary hypercorticoidism (Cushing's disease), the patients with elevated adrenal gland hormones level underwent a high-dose overnight dexamethasone suppression test (DST).

Blood pressure was thoroughly measured before the surgery and intraoperatively to control hemodynamics in the time of operation and especially during adrenal gland manipulation.

THE AIM

To optimize the indications for partial laparoscopic adrenalectomy (PLA), to give a detailed outline of a PLA technique and to provide technical tips to ensure safe and highly-effectiveness, based on the knowledge of adrenal anatomy and blood supply.

MATERIALS AND METHODS

Between January 2010 and September 2018, our department performed 47 adrenal glands surgeries. The operations included 29 total laparoscopic adrenalectomies (TLA), 4 open adrenalectomies (OA) and 14 partial laparoscopic adrenalectomies (PLA). The surgeries on the right side made 27 (57%) case, while those on the left side made 20 (43%) ones. The median age of the patients was 63 ± 12 years, and their gender breakdown was 16 (34%) male and 31 (66%) female. The indications for OA included primary malignant tumors exceeding 6 cm as well as retrocaval location of the tumor. The PLA was performed for benign tumors from 1.5 to 4 cm large and for cysts with size up to 8 cm. The left-sided PLA was performed in 8 (57%) cases, and right sided – in 6 (43%) cases. Technically, it was possible to perform the left-sided PLA in a bigger number of patients. It can be explained by a different location of the major left adrenal vein and a more stretched adrenal gland.

RESULTS AND DISCUSSION

As a rule, the right-sided PLA is more difficult to perform due to a shorter major adrenal vein. However, we discovered that the presence of additional veins to right adrenal gland enabled us to save more adrenal gland tissue with good blood supply, which in our investigation had

been detected in 25% patients (Figure 2). The PLA was performed with "cold" scissors following the preliminary clipping of resection border. The clipping was performed with large Hem-o-lok clips. N. Roukounakis [10] suggest reaching 3-5 mm of resection border. A traditional way of adrenal gland resection with electrocoagulation ligation has a serious disadvantage, lying in coagulation necrosis in resection margin, which reduces the volume of the adrenal gland functional tissue.

The patient is placed in lateral position at an angle of 60˚; a soft roll may be placed under rib XI. 3-4 ports are used for the left-sided operation and 4 – for right-sided operation, including liver retractor. This operation employs 30-degree optical equipment. Following the pneumoperitoneum creation with the help of Veress needle, an 11-mm port is placed in the gap between costal arch and lateral margin of abdominal rectus muscle. It is also possible to perform the first port placement according to Hasson technique [11], which is especially beneficial in the case of repeated abdominal cavity surgery. Further, a 30-degree laparoscope is inserted and primary visual investigation of 4 abdomen quadrants is performed. After that, all ports are placed under visual control. Under direct visual control, the 11-mm port for liver retractor is placed on linea axillaris media. The 11-mm port is placed on linea medioclavicularis in infracostal region. Finally, following the liver retractor installation and retraction of the liver, the most medial 11-mm port is placed on linea parasternalis. To operate on left adrenal gland, it is possible to use a 6-mm port placed in the same place as the median 11-mm port is placed for right-sided operation (Figure 3), because in the most cases it is not necessary to use 10-mm tools for the left hand. To avoid an instrumental conflict, the distance between the ports has to be at least 5 cm.

On the left side, the descending colon and the spleen have to be fully mobilized. Colon, spleen and pancreas are mobilizing medially until the adrenal gland is fully visualized. A special attention has to be paid to the pancreas tail, which in some cases can be mistaken for the adrenal gland. Leaning on the PLA experience gained in our clinic, we always try to achieve the maximal pancreas tale mobilization to be able to fully visualize the medial border of the adrenal gland. This technique helps to better assess the adrenal gland anatomy, the peculiarities of its blood supply and use these findings for a more effective planning of anatomical resection.

On the right side, a triangular ligament of the liver is dissected maximally cranially to ensure a liver mobility. The liver is retracted upward with the help of the liver retractor. Following liver retraction, it is possible to access to the right adrenal gland without colon mobilization. For better visualization of inferior vena cava, duodenum is mobilizing medially. To avoid a duodenum damage, the use of coagulation has to be minimized.

Following the tumor resection border assessment, adrenal gland tissue is clipped with big Hem-o-lok clips, leaving roughly 0.2 – 0.5 cm to the visible tumor border along the entire length (Figure 4). The safety margin has not yet been determined. Keeping in mind the fact that partial adrenalectomy is commonly indicated in the case of small benign tumors, we believe that under sufficient visualization of tumor border, "protective" margin of 2 mm of intact tissue is sufficient to prevent a false tumor relapse. Klaus J. [12] offers to reach hemostasis using bipolar coagulation and fibrin glue. The "cold" scissors resection after preliminary clipping makes it possible to better control the resection margin, as opposed to coagulation hemostasis. Preliminary clips-assisted tumor isolation also helps to prevent catecholamines ejection into the blood, which can cause a poorly treated hypertensive crisis. In relation to partial adrenalectomy,

G. Cavallaro [13] offers to ligate preliminary adrenal vein, yet, our approach makes it possible to avoid ligation. The tumor is extracted from the wound with a container. Blake Drain 18 Fr is applied to the resection area for 24 hours.

In the preoperative period, the patients with hormone-producing tumors received alpha-blockers for 2 weeks. Antibiotic prophylaxis was performed intraoperatively. In early postoperative period, thromboprophylaxis was performed according to the current international guidelines. Analgesic infusion was necessary only within the first 12 hours after the operation. Enteral feeding starts 10 hours after operation.

The histopathological examination of all operated patients (Table 1) detected 9 (19.1%) malignant tumors, including 5 metastatic tumors (4 cases of lung tumor metastasis and 1 uterine carcinoma metastasis). Benign tumors includes 24 (63%) adenomas, 8 (21%)

pheochromocytomas, 4 (10,5%) cysts and 2 (5,5%) ganglioneuromas. Post-PLA

histopathological findings revealed 6 adenomas, 2 pheochromocytomas, 4 cysts and 2 ganglioneuromas. The median TLA time was 70 min. (60-80 min), PLA – 60 min. (50-70 min.). No significant operation time difference between TLA and PLA groups was detected. (p>0,8). The median blood loss was 80 ml (50-250 ml) in TLA and 50 ml (20-80 ml) in PLA (p>0,05).

One case of postoperative complication was a post-TLA bleeding (**Clavien-Dindo III**), which necessitated re-intervention and endoscopic hemostasis. The symptoms of hypercorticism (**Clavien-Dindo II**) were detected in one post-TLA patient, were managed conservative. Nothing like this was detected in any PLA case. Local recurrence was not observed during a follow up (4-53 month) in both groups.

In this paper, we described a standardized step-by-step technique of partial laparoscopic adrenalectomy, which can be performed effectively and safety.

As any other surgery, PLA requires a thorough patient selection, which is essential particularly for an experience gaining surgeon.

The profound knowledge of left-sided and right-sided PLA is the best tool to minimize intraoperative complications. On the left side, left renal vein, pancreas tale, kidney upper pole and m. psoas can significantly facilitate an operative visualization. As for the right side, it is necessary

to visualize inferior vena cava, right renal vein, kidney upper pole and m. psoas. Identification and visualization of blood vessels are the most difficult part of the adrenal gland surgery. Special attention has to be focused on the blood supply anatomy in the right-sided PLA.

CONCLUSIONS

Keeping in mind anatomical features of adrenal gland blood supply in highly-selected patients, PLA can be performed in a number of patients. 2 mm of a minimal resection margin is enough to preserve a false tumor recurrence. Anatomically grounded PLA is becoming a new standard of benign adrenal gland tumors treatment, providing an opportunity to save more adrenal gland functional tissue and to prevent hipocorticism development in postoperative period, which is particularly important for hereditary and bilateral tumors.

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ORCID and contributionship:

Sergiy P. Styopushkin: 0000-0001-7841-2484 [A, C, E, F]
Viktor P. Chaikovskyi: 0000-0001-7974-3656 [A, B, C, D]
Volodymyr A. Chernylovskyi: 0000-0002-5795-1574 [A, B, C, D, E, F]
Ruslan V. Sokolenko: 0000-0002-9083-4177 [A, B]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Volodymyr A. Chernylovskyi
City Clinical Hospital №4 "DRU"
31 Blizhnaya st., 49000 Dnipro, Ukraine
tel: +380973695672
e-mail: chernylovskyi@gmail.com

Received: 12.11.2019
Accepted: 26.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

HEMATOLOGICAL CHANGES AFTER INTRODUCTION OF DIFFERENT SIZES LEAD NANOPARTICLES (IN EXPERIMENT)

DOI: 10.36740/WLek202009216

Inna V. Gubar[1,2,3], Olena L. Apykhtina[2], Oleksandr P. Yavorovsky[1], Oleksandr I. Kovalchuk[3], Svitlana M. Chukhray[1], Liudmyla M. Sokurenko[1,3]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE, KYIV, UKRAINE
[3]TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, KYIV, UKRAINE

ABSTRACT

The aim: was to compare the changes in hematological parameters of blood in the conditions of prolonged exposure of lead sulfide nanoparticles (NP) of different sizes and of lead nitrate.

Materials and Methods: The study was conducted on mature male Wistar rats 160-180 g, intraperitoneally injected with $Pb(NO_3)_2$ and NP PbS of 26-34 nm and 50-80 nm in 0,94 mg/kg/day dose adjusted to lead. Toxic effects were evaluated after 1,5 months, 3 months and 1 month after exposure. The studies were performed on hematologic analyzer.

Results: Changes in peripheral blood were characterized by decrease in the hemoglobin level in the blood. An increase in the total number of leucocytes was observed, which is statistically significant by the increase of number of lymphocytes and the absolute number of monocytes. Changes in the platelet number were characterized by an increase in the average volume of platelets and a decrease in the platelet heterogeneity index.

Conclusions: The most pronounced changes hemoglobin level in the blood and concentration of hemoglobin in the erythrocyte were observed in the effects of PbS NP (50-80 nm), but leucocytes indicators - of PbS NP (26-34 nm) and $Pb(NO_3)_2$.

KEY WORDS: lead, nanoparticles, hematological parameters, hematotoxic effect

Wiad Lek. 2020;73(9 p. II):1986-1993

INTRODUCTION

Among the chemicals that pollute objects of the environment, heavy metals and they compounds form a significant group of toxicants [1 - 6]. Lead, as one of the most widespread and highly toxic metals, is included by World Health Organization and other international organizations in the list of global pollutants. The toxic effect of lead and its compounds on the body is manifested predominantly by damage to the nervous, cardiovascular, blood and kidney systems, and a violation of porphyrin metabolism [7 - 11].

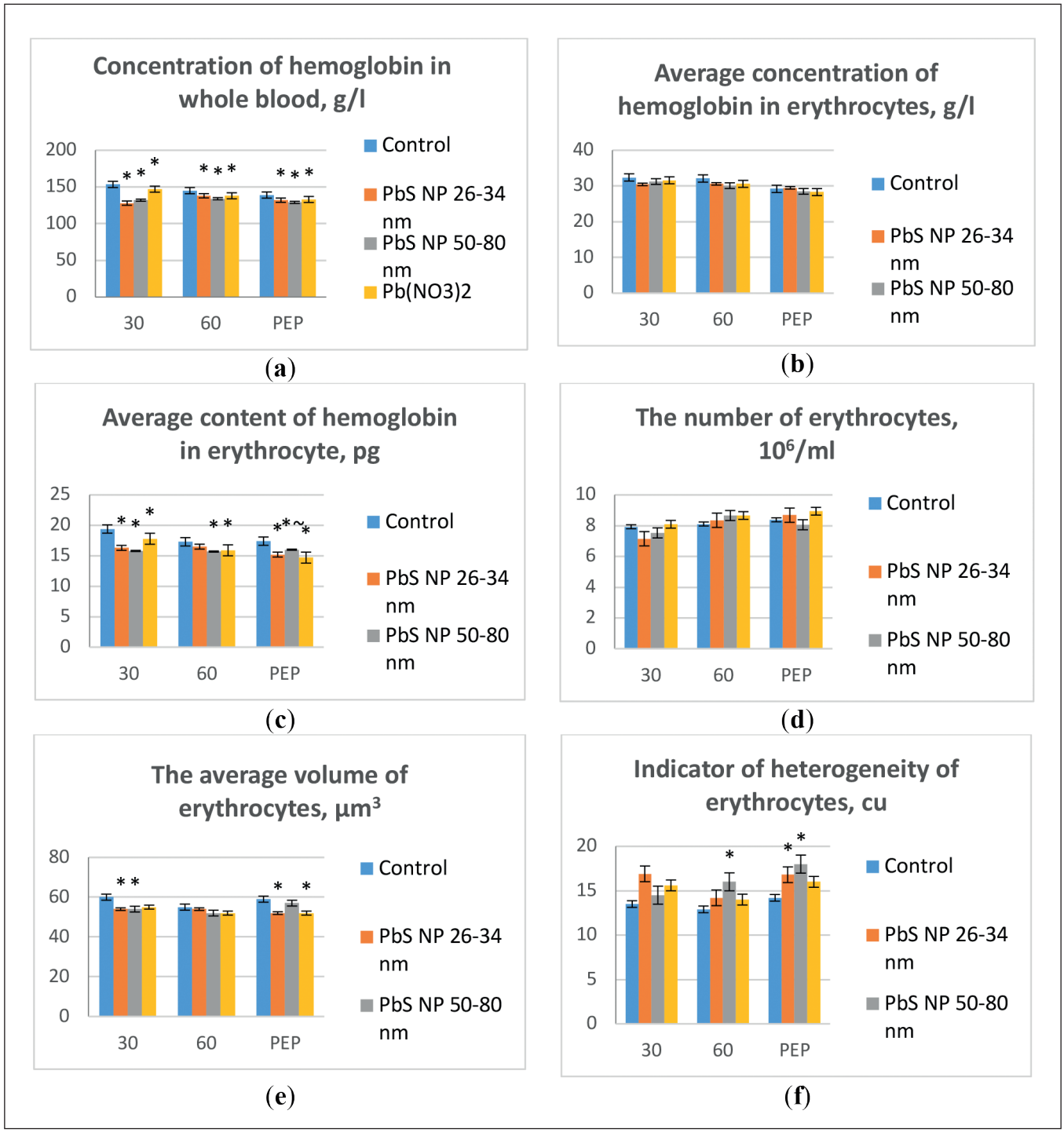
A classic manifestation of the negative effects of lead on the body is the development of anemia due to damage to the organs of the hematopoiesis. It is known that lead that has got into the respiratory tract and/or into the gastrointestinal tract, enters to the bloodstream after a few minutes. Blood cells are among the first to get the negative impact of lead.

Lead, even in the short-term intake in the body at relatively low doses, causes a pronounced hematotoxic effect characterized by a violation of hemopoiesis and morphofunctional changes in all of the formed blood elements, the result of which is the emergence of anemia and the development of hypoxia in the organism, activation of free radical oxidation and oxidative stress, which causes the implementation of vaso-toxic action of the metal [12, 13].

The development of nanotechnology is a promising industry in the modern information world [14]. When the particles of lead compounds are reduced to nanometers, their optical and quantum-chemical properties change significantly which contributes to the widespread implementation of nanoparticles (NP) of lead compounds in various industries and provides an opportunity to improve already existing as well as create more sensitive devices [15].

Lead sulfide in a nanocrystalline state has been widely used in infrared optics as a material for the manufacture of temperature-sensitive sensors, detectors, photoconductors, selective sensors; in flexible optoelectronics – high-performance photodetectors; in solar elements of the third generation in the form of quantum dots, which greatly increases the efficiency of the transformation of solar energy; as well as in a variety of polymer films and nanoporous matrices [16, 17].

However, the widespread use of specific properties of lead nanoparticles and its compounds not only opens up new perspectives, but can also pose a danger both to human health and to the environment [18 - 21]. The lack of thorough knowledge about the degree of lead nanoparticles toxicity and its potential danger to the organism requires a wide range of medical and biological research [22 - 24], in particular, the study of hematotoxic activity in evaluating the toxic properties of new compounds and NP which containing lead.



Note: * – statistically significant differences between the rates of animals in experimental groups from and of the control group; # – statistically significant differences between the indicators of the groups of animals exhibited by lead sulfide NP of different sizes; ~ – statistically significant differences between the indicators of the groups of animals exhibited by lead sulfide NP and lead nitrate.

Figure 1. Changes in parameters of the erythrocytes of peripheral blood cells of experimental animals.

THE AIM

The aim of the study was to compare the changes in hematological parameters of blood of experimental animals in the conditions of prolonged exposure of lead sulfide NP of various sizes and lead nitrate (ionic form).

MATERIALS AND METHODS

In this work are used lead compounds in nanoform: NP of lead sulfide (NP PbS) with 26-34 nm and 50-80 nm average size and in ionic form: lead nitrate ($Pb(NO_3)_2$) which is readily soluble in water. Lead sulfide NP was obtained by

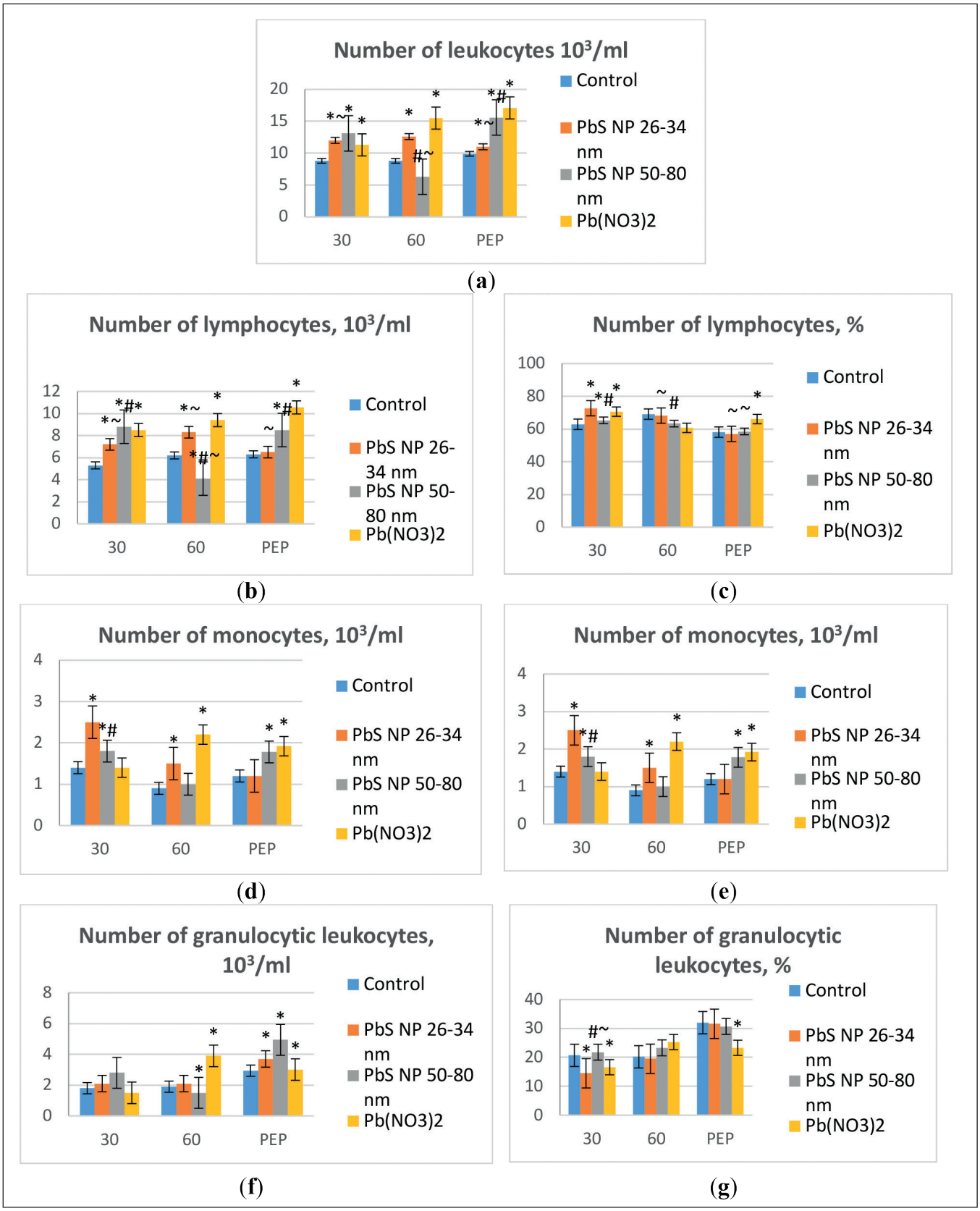


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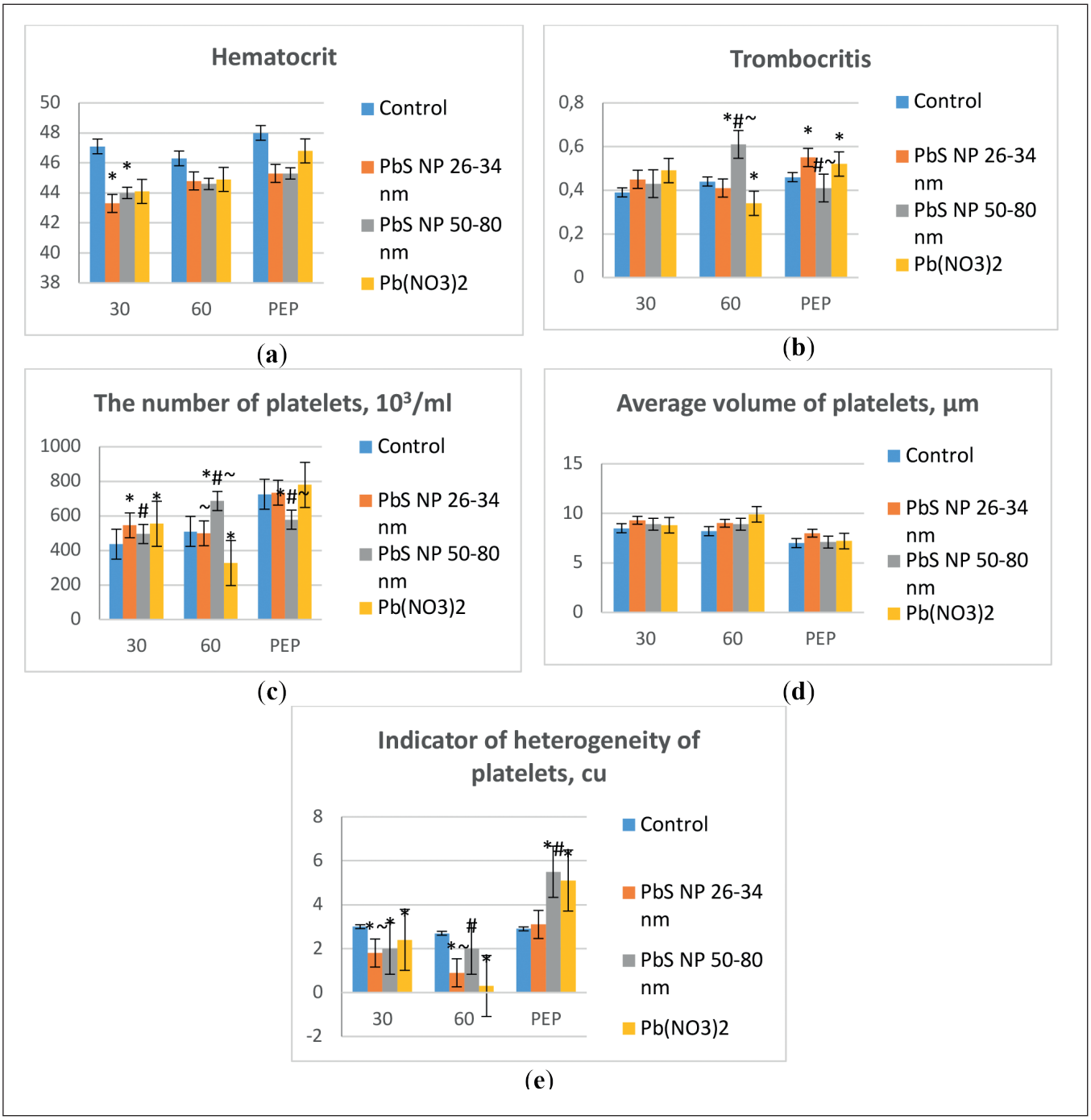
Figure 2. Changes in the parameters of the leukocytes of peripheral blood cells of experimental animals.



Note: * – statistically significant differences between the rates of animals in experimental groups from and of the control group; # – statistically significant differences between the indicators of the groups of animals exhibited by lead sulfide NP of different sizes; ~ – statistically significant differences between the indicators of the groups of animals exhibited by lead sulfide NP and lead nitrate.

Figure 3. Changes in hematocrit and platelets of peripheral blood levels of experimental animals.

chemical synthesis using a sodium polyphosphate stabilizer $(NaPO_3)_n$. NP size was determined by electron microscopy.

The study was conducted on mature male Wistar rats 160-180 g. The animals were kept in vivarium on a standardized diet with free access to drinking water. The rats were divided into 3 experimental groups and control group. The first experimental group was injected with NP PbS 26-34 nm in size, the second – NP PbS 50-80 nm in size, the third – with $Pb(NO_3)_2$; the control group received a physiological solution. These substances were administered intraperitoneally daily 5 times a week (simulation of a working week) in 0,94 mg/kg/day dose adjusted to lead. Toxic effects were evaluated after 30 injections (1.5 months) and 60 injections (3 months) - subchronic experiment and in the postexposure period (1 month after cessation of exposure). The blood was taken immediately after decap-

itation. The studies were performed on the ABX MICROS 60 hematologic analyzer in accordance with the manufacturer's instructions. Statistical processing of primary data was carried out using the program Microsoft Excel 2003 and SPSS 21.0. Statistical significance of differences between indices was evaluated by Mann-Whitney U-test.

The studies were performed within the frame of research of State Institution Institute for Occupational Health of NAMS of Ukraine: «Comparative toxicity of micro- and nanoparticles of lead in experiments in vitro and in vivo (to the problem of improving the principles and methods of toxicological and hygienic studies of heavy metals)» (State registry number 0110U000299), «Investigation of the toxic effects of heavy metal nanoparticles, search and substantiation of preventive measures » (State registry number 0116U000497).

All manipulations with animals were carried out in accordance with the provisions of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1985). The study meets bioethical requirements. The experiment plan is approved by the Bioethics Commission State Institution «Institute for Occupational Health of NAMS of Ukraine, Kyiv» (Minutes № 5, session of bioethics commission from 23.11.2017).

RESULTS

The results of conducted experimental studies indicate that after subchronic experiment of lead compounds to experimental animals there were changes in the erythrocytes (fig. 1). A statistically significant reduction of hemoglobin concentration in blood (compared to the corresponding indicators of control group) was detected after the injection of lead nitrate and lead sulfide in the form of nanoparticles, which may indicate a violation of the heme synthesis processes.

In the post-exposure period (PEP), hemoglobin level was also reduced in all three experimental groups. After subchronic experiment of lead compounds to rats, the average content of hemoglobin in erythrocyte (per unit volume of the cell) was significantly lower in animals of all three experimental groups, moreover with action of the NP PbS this indicator was significantly lower than with action of lead nitrate. One month after the cessation of exposure, a significant decrease in this index was observed in animals exposed of lead nitrate and NP PbS with smaller size (26-34 nm).

In animals, exposed with studied lead compounds in nano- and ionic forms, there were no statistically significant changes in the number of erythrocytes.

The average volume of erythrocytes in the first study period was reduced in the blood of animals of all three experimental groups compared with control parameters indicating the outflow in the vascular bed of functionally immature erythrocytes. After the recovery period (1 month), the average volume of erythrocytes was statistically significantly lower in animals exposed of lead nitrate and of NP PbS with smaller size.

Indicator of heterogeneity of erythrocytes which characterizes the degree of heterogeneity of erythrocytes by their size, was increased in animals of all three experimental groups compared with the control group. NP PbS of 50-80 nm caused more pronounced statistically significant morphological changes in red blood cells of animals than other compounds.

In the post-exposure period, the erythrocyte heterogeneity index was also elevated in the blood of animals in all three experimental groups compared with the control parameters, but was most changed by the action of PbS NP of larger size. Thus, changes in the erythrocyte series of blood cells of rats exposed of PbS NP of different sizes were characterized by a decrease of hemoglobin level in the blood, a decrease in the content and concentration of hemoglobin in the erythrocyte, which indicates a violation of the processes of hemoglobin synthesis

Reducing the volume of red blood cells and increasing the heterogeneity of erythrocytes indicates the violation of the erythropoiesis processes and the output in the vascular bed of functionally immature and poor on hemoglobin erythrocytes. The most pronounced changes in the blood of rats were observed with the effect of PbS NP with larger size compared with smaller PbS NP and lead nitrate.

Indicators of leukocyte series of peripheral blood cells of rats after exposure to lead compounds were characterized by certain changes (Fig. 2).

In animals there was a tendency to increase the number of leukocytes in comparison with the control group, but it was not statistically significant. The number of lymphocytes in the blood, both absolute and relative, increased statistically significantly after 30 days of exposure in animal from experimental groups, but the most significant changes occurred after injection of a smaller PbS NP and lead nitrate. In the post-exposition period, there was a normalization of the level of lymphocytes in the blood of experimental groups of rats relative to the control group of animals. In the blood of rats exposed to PbS NP and lead nitrate, there was a statistically significant increase of the absolute number of monocytes, while the relative number of monocytes decreased, which was due to an increase in the number of lymphocytes in the leukocyte formula. At the end of the recovery period, in experimental rats of all groups there was observed approximation of the number of monocytes to control levels. There were no significant changes in the number of neutrophils in the experimental animals both after subchronic experiment and in the post-exposure period.

Hematocrit was statistically significantly lower in the blood of animals after exposure to lead compounds with respect to control in the first study period, and 1 month after the cessation of exposure was not statistically different from the control values. The rate of thrombocyte in the blood of animals in experimental groups was not statistically different from the rate of the control group in both research periods (Fig. 3).

The number of platelets in the first study period of the animals' blood exposed to lead compounds was not sta-

tistically different from the control values. In the post-exposition period, platelet count decreased in animals after the introduction of a larger PbS NP. The average platelets volume in animal blood in experimental groups in both monitoring periods increased with respect to control, but a statistically significant change was observed in the rats exposed to smaller PbS NP.

The platelet heterogeneity index, which characterizes the thrombocytes volume distribution in the blood of animals in experimental groups, decreased with respect to control group in both studies, but these changes were statistically significant in the post-exposure period, especially in the effect of smaller PbS NP. An increase in the average volume of platelets is due to accelerated thrombocytopoiesis (young blood platelets have a larger volume), this is also confirmed by the decrease in platelet heterogeneity. Thus, changes by the effects of a smaller PbS NP after the restoration period are observed due to accelerated thrombocytopoiesis and the output of young, functionally immature blood platelets in the bloodstream. At the same time, these changes are adaptive in nature. After injections of larger PbS NP, these changes are less pronounced, and there is a decrease in platelet count. The latter indicates a breakdown of compensatory mechanisms and a more negative impact of the PbS NP on thrombocytopoiesis.

DISCUSSION

The obtained results allow to state that after injections of lead compounds, changes in the peripheral blood of rats were characterized by a decrease in the level of hemoglobin in the blood, decrease in the content and concentration of hemoglobin in the erythrocytes indicating a violation of the processes of hemoglobin synthesis and a decrease in the volume of erythrocytes and an increase in the heterogeneity of erythrocytes, that indicates a violation of the processes of erythropoiesis and the exit to the vascular bed of the functionally immature erythrocytes poor on hemoglobin. The most pronounced changes in the peripheral blood of rats were observed in the effects of PbS NP with a larger size (50-80 nm) compared to a smaller PbS NP (26-34 nm) and lead nitrate (ionic form).

Indicators of the leukocyte series of peripheral blood cells of rats were characterized by a slight increase in the total number of leukocytes, significant increase in the absolute and relative number of lymphocytes and the absolute amount of monocytes. The most significant changes occurred after injections of a smaller PbS NP and lead nitrate.

Changes in the platelet count of blood cells were characterized by an increase in the average volume of platelets and a decrease in the platelet heterogeneity index. Under the influence of PbS NP (26-34 nm) in the post-expositional period, changes are observed due to accelerated thrombocytopoiesis and the release of young, functionally immature blood platelets to the bloodstream. At the same time, these changes were adaptive in nature. These effects were less pronounced under the influence of PbS NP (50-80 nm), but there was a decrease in platelet count, indicating a breakdown of compensatory mechanisms and a more negative influence on thrombocytopoies.

The obtained data testify that the toxic effect of the PbS NP is conditioned by the negative influence of lead on the organism, which is consistent with the data on the study of the mechanism of its hematotoxic action [25]. The results of studies [26] show that lead inhibits enzymes of haem biosynthesis and alters haematological parameters of battery manufacturing workers, which confirms our experimental data (after injection of lead compounds, changes in the peripheral blood of rats were also characterized by a decrease in hemoglobin levels in the blood, a decrease in the content and concentration of hemoglobin in the erythrocyte, a decrease in the volume of erythrocytes and an increase in the total number of leukocytes).

The results of our experimental studies on changes in the leukocyte series of peripheral blood cells of rats (increase in the number of monocytes and lymphocytes) were also confirmed in the data obtained by V.A. Kondratyuk [27] with oral administration of lead NP to rats at doses of 7 mg/kg of body weight against the background of drinking water of various composition.

Toxicological studies of Asghar Amiri [28] shows increasing of Pb nanoparticles toxicity compared to micrometer particles of the same composition with a single intravenous injection of PbO and PbO-NPs to rats at doses of 5 mg/kg of body weight (once a week for 8 consecutive weeks), which is consistent with our results.

The dynamics of the content of alanine aminotransferase (ALT) and aspartate aminotransferase (AsAT) in the blood serum of experimental animals demonstrates a statistically significant decrease in the activity of enzymes on 30 injections and increase on 60 injections. This is evidence of compensatory processes with toxic effects of Pb (NO3) 2, PbS NP with a larger size (50-80 nm) and small size (26-34 nm) on hepatocyte [29].

CONCLUSIONS

1. The study was conducted on mature male Wistar rats in a subchronic experiment: 30 and 60 injections $Pb(NO_3)_2$ and PbS NP of 26-34 and 50-80 nm during 1,5 and 3 months five times a week in 0,94 mg/kg/day dose adjusted to lead and in the end of the recovery period (1 month) revealed a change in the hematological parameters of the animals.
2. After injections of lead compounds, changes in peripheral blood of rats were characterized by a decrease in hemoglobin levels in the blood, a decrease in the content and concentration of hemoglobin in the erythrocyte, indicating a violation of the processes of hemoglobin synthesis, and a decrease in the volume of erythrocytes and an increase in the heterogeneity of erythrocytes, that shows a violation of the processes of erythropoiesis and the exit to the vascular bed of the functionally immature erythrocytes poor on hemoglobin. The most pronounced changes in peripheral blood of rats were observed in the effects of PbS NP (50-80 nm) compared with smaller PbS NP (26-34 nm) and $Pb(NO_3)_2$ (ionic form).

3. For indicators of the leukocyte of peripheral blood cells of rats, a small increase in the total number of leukocytes was found, which is statistically significant with an increase in the absolute and relative number of lymphocytes and the absolute amount of monocytes. The most significant changes occurred after the introduction of PbS NP (26-34) nm and $Pb(NO_3)_2$.
4. Changes in the platelet count of blood cells were characterized by an increase in the average volume of platelets and a decrease in the platelet heterogeneity index. Under the influence of PbS NP (26-34 nm) in the post-expositional period, changes were observed due to accelerated thrombocytopoiesis and the release of young, functionally immature blood platelets in the bloodstream. At the same time, these changes had a compensatory adaptive nature. By the effects of PbS NP (50-80 nm), these changes were less pronounced, however, there was a decrease in platelet count, indicating a breakdown of compensatory mechanisms and a more negative effect on thrombocytopoiesis.

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ORCID and contributionship:
Inna V. Gubar: 0000-0002-4105-5644 [A, B, D]
Olena L. Apykhtina: 0000-0003-3677-3921 [C]
Oleksandr P. Yavorovskiy: 0000-0002-4573-8039 [E, F]
Olexandr I. Kovalchuk: 0000-0002-6311-3518 [E]
Svetlana N. Chuhray: 0000-0001-7431-7375 [E]
Liudmyla M. Sokurenko: 0000-0002-6870-2290 [D, F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Inna V. Gubar
Bogomolets National Medical University
13 T. Shevchenko st., 01601 Kyiv, Ukraine
tel: +380679838791
email: ginna5@ukr.net

Received: 09.09.2019
Accepted: 25.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

THE EFFECT OF A-LIPOIC ACID ON THE FUNCTIONAL STATE OF PERIPHERAL NERVE FIBERS IN POLYNEUROPATHY OF THE LOWER EXTREMITIES IN PATIENTS WITH CHRONIC HEMOBLASTOSIS

DOI: 10.36740/WLek202009217

Oleksandra O. Piddubna, Nataliya V. Lytvynenko, Anzhelina M. Krivchun, Kateryna A. Taryanyk
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

The aim: To evaluate the effectiveness of the appointment of α- lipoic acid for correcting electroneuromyographyc indicators polyneuropathy of the lower extremities in patients with hemoblastosis.

Materials and methods: The study included 77 patients from hematology department of Poltava Regional Hospital, who were divided into 3 groups according to the underlying disease: Group 1 - patients with chronic myeloid leukemia (CML) (n = 26) groups and 2 - patients with chronic lymphocytic leukemia (CLL) (n = 27), group 3 - patients with multiple myeloma (MM) (n = 24). For the examined patients were taken electroneuromyographyc researches of distal lower extremities by measuring the following parameters: the amplitude of the M-response from short extensors nerves of the fingers (MEDB) and abductor of the big toe (MAH) and the rate of excitation the spread of short extensors nerve of the fingers (VEDB), thumb abductor (VAH), superficial shallow (VSF) and calf (VC) nerves on both sides (sin/dex) before and after administration of α- lipoic acid.

Results: ENMG examination of the peripheral nerves of the lower extremities in patients with CML and CLL revealed a slight decrease in M-responses at normal values of the rate of conduction of excitation through sensory and motor fibers. In patients with MM, multiple lesions of peripheral nerve fibers of the lower extremities were detected, which is represented by a decrease in the M-response and the rate of excitation through sensory fibers and indicates deeper lesions, namely the axial cylinder, which requires longer treatment. The difference in the dynamics of the studied indicators indicates a different degree of PNP. Administration of α-lipoic acid increased the M-response rate and the rate of excitation of motor fibers in all groups of patients. The rate of excitation through sensory fibers was improved in patients with CLL and MM. Following the use of α-lipoic acid in the complex treatment of patients with MM ENMG, the signs of peripheral nerve fiber damage in the lower extremities were worse due to the severe initial condition, but reached a medium level. The positive effect of α-lipoic acid can be caused by a decrease in oxidative stress and endothelial dysfunction in nerve vessels, and, as a consequence, an improvement in the trophism and functional state of nerve fibers.

Conclusions: ENMG signs of defeat of PNP of the lower extremities are more expressed at MM. The appointment of α-lipoic acid in the complex treatment of PNP in patients with chronic hemoblastosis improves the functional state of the peripheral nerve fibers of the lower extremities and may be a component of pathogenetic therapy.

KEY WORDS: Chronic hemoblastosis, peripheral nervous system, polyneuropathy, electroneuromyographic, α-lipoic acid

Wiad Lek. 2020;73(9 p. II):1993-1997

INTRODUCTION

Hemoblastosis is the collective name of neoplastic diseases of the blood system, which are malignant neoplasms from cells of hematopoietic and lymphatic tissues with involvement in the process of a number of organs and body systems. They account for more than 1/3 of all tumors in the population and are the leading cause of death among all diseases of the blood system [1-8]. Neurological disorders in patients with hematologic diseases (PHD) are classified as the secondary lesions of the nervous system (NS). Attachment of neurological symptoms to the main symptoms of hemoblastosis significantly increases the severity of the patients' condition and affects the outcome of treatment [9, 10]. In recent years, in the process of PHD monitoring, there has been an increase in the frequency of peripheral nervous system (PNS) lesions, not only during specific treatment, but also at the stage of diagnosis. Polyneuropathy (PNP) is the most common lesion of PNS. Depending on the pathogenesis, peripheral neuropathies in diseases of the blood system can be divided into 4 groups: specific metabolic disorders in the nervous system; compression of nerves; infiltration of peripheral nerves by mast cells; toxic medicinal polyneuropathies [11]. Post-chemotherapy polyneuropathy (HTPNP) is a specific systemic manifestation of neurotoxicity that affects both the quality of life of cancer patients and the possibility of anticancer treatment. According to a number of literature sources, chemotherapy-induced polyneuropathy occupies the first place in the structure of PNS lesions and is on average 40-60% [12-14]. Therefore, in chronic hemoblastoses (hml, hlm, mm), the clinical manifestations of PNP from the very beginning of the disease are so variable that in most cases for the diagnosis of PNP, electroneuromyographic (ENMG) research is crucial diagnostic value, as noted by many authors and diagnoses peripheral nerves, which allows evaluating their functional characteristics [15-18]. According to the results of clinical studies at ENMG examination of patients with MM, it was found a decrease in the amplitude of muscle

responses (M-responses) in the stimulation of the tibial nerves, the action potential of the calf nerves, the amplitude of the evoked cutaneous sympathetic potential from the feet, and the increase in sympathetic volume. potential, reduction of the speed of propagation of excitation on the motor and sensory fibers of the tibial and calf nerves. Thus, according to ENMG, signs of motor-sensory-vegetative PNP were detected in the legs of the axon-demyelinating type, mainly axonal with secondary demyelination [19]. It should be noted that to date, there is no conclusive data on ENMG examination of patients with CML and CLL. Thus, the problem of timely diagnosis of the diagnosis and treatment of CTPD in chronic hemoblastoses is extremely important for improving the quality of life of patients.

THE AIM

The aim was to evaluate the effectiveness of the appointment of α- lipoic acid for correcting electroneuromyographyc indicators polyneuropathy of the lower extremities in patients with hemoblastosis.

MATERIALS AND METHODS

The study included 77 patients from hematology department of Poltava Regional Hospital, who were divided into 3 groups according to the underlying disease: Group 1 - patients with chronic myeloid leukemia (CML) (n = 26) groups and 2 - patients with chronic lymphocytic leukemia (CLL) (n = 27), group 3 - patients with multiple myeloma (MM) (n = 24). Inclusion criteria: the presence of CML, CLL, MM; at least 1 course of chemotherapy (CT); age more than 18 years. Exclusion criteria: other hematologic diseases; undergoing the first course of chemotherapy; age under 18years; increased sensitivity to α- lipoic acid preparations. All patients were treated according to standard protocols due to the underlying disease and received 600 mg of α- lipoic acid twice daily for 6 months. Patients were given written informed consent to conduct the research following the recommendations of the ethics committee questions of biomedical research and the Helsinki Declaration.

For the examined patients were taken electroneuromyographyc researches of distal lower extremities by measuring the following parameters: the amplitude of the M-response from short extensors nerves of the fingers (MEDB) and abductor of the big toe (MAH) and the rate of excitation the spread of short extensors nerve of the fingers (VEDB), thumb abductor (VAH), superficial shallow (VSF) and calf (VC) nerves on both sides (sin/dex) before and after administration of α- lipoic acid. Statistical analysis was performed using IBM SPSS Statistics 23.0. The Shapiro-Wilk test was used to evaluate the normality of quantitative distribution. The results are presented as mean values (M) and root mean square deviations (σ) or median (Me) and interquartile (25% - 75%) span (Q1-Q3) depending on the distribution. For data that is subject to the normal distribution used single-factor analysis of variance ANOVA with Bonferroni correction. If the distribution was different from the normal, the Crackel-Wallis test was used, followed by a posteriori analysis by the Dan criterion. Comparisons of pre- and post-treatment data were performed using Student's t-test for related samples in the case of normal distribution and Wilcoxon's criterion for distribution other than normal. The results were considered statistically significant at $p < 0.05$ and posterior comparisons at $p < 0.017$.

RESULTS AND DISCUSSION

In group 1 (mean age 54 ± 15.76), the duration of the disease was 1.5 (1-4) years and the number of courses of CT was 1 (1-2). In group 2 (mean age 59.96 ± 10.57) these indicators were 2 (1-4) years and 2 (1-3) courses, respectively. Group 3 patients (mean age 58.33 ± 6.17) had 2 (1-3) years of an underlying disease and received 2 (1-3) courses of CT. There were no statistically significant differences between the indicators, which makes it possible to compare these groups and eliminate the influence of potential confounders.

The M-response amplitudes in treatment groups 1 and 2 were below the normal range (3–5 mV) and were in group 1: MEDBsin - 3.01 (2.48-3.19) mV, MEDBdex - 3.12 (2.62-3.53) mV, MAHsin - 3.25 (2.49-4.52) mV, MAHdex - 3.57 (2.49-4.91) mV, and group 2: MEDBsin - 3.12 (2.23-3.56) mV, MEDBdex - 3.12 (2.47-3.65) mV, MAHsin - 3.24 (2.45-4.12) mV, MAHdex - 3.23 (2.48-3.95) mV. In group 3 the indicators were below the norm and were determined at the following level: MEDBsin - 2.83 (1.4-3.13) mV, MEDBdex - 2.86 (1.49-3.11) mV, MAHsin - 2.57 (1.1-3.11) mV, MAHdex - 2.75 (1.3-3.41) mV. There were not found statistically significant differences between groups 1 and 2. A significant decrease in MAHsin in group 3 was noticed by 21.9% compared to group 1 and by 20.8% to group 2, as well as MAHdex decreased by 23% and 14.9%, respectively. The study of the amplitude of the M-response after the appointment of α- lipoic acid in all groups was within the normal values, namely in group 1: MEDBsin - 3.08 (2.56-3.47) mV , MEDBdex - 3.39 (2.88-3.91) mV, MAHsin - 3.39 (2.91-4.68) mV , MAHdex - 3.61 (2.98-5.01) mV, in the group 2: MEDBsin - 3.38 (2.84-3.89) mV, MEDBdex - 3.29 (2.79-3.87) mV, MAHsin - 3.61 (2.94-4.48) mV, MAHdex - 3.45 (2.93-4.12) mV, and in group 3: MEDBsin - 3.24 (2.57-3.91) mV, MEDBdex - 3.3 (2.55-3.96) mV, MAHsin - 3.07 (2.51-3.98) mV, MAHdex - 3.37 (2.68-4.06) mV. Significant increases were observed in all groups and, as a consequence, their rise to normal in group 3 after treatment. There was not detected a statistically significant difference between the groups after treatment. These changes are presented in figure 1.

Velocity of motor excitation on motor fibers before treatment was within the normal range (40-60 m/s) in all groups, namely group 1: VEDBsin - 50.87 (48.84-52.11) m/s , VEDBdex - 50.61 (48.0-53.41) m/s , VAHsin - 51.12 (45.33-52.5) m/s , VAHdex - 52.25 (49.28-53.13) m/s; in group 2: VEDBsin - 52.14 (48.3-57.12) m/s , VEDBdex - 53.21 (46.14-57.15) m/s , VAHsin - 52.12 (48.69-58.32) m / s ,

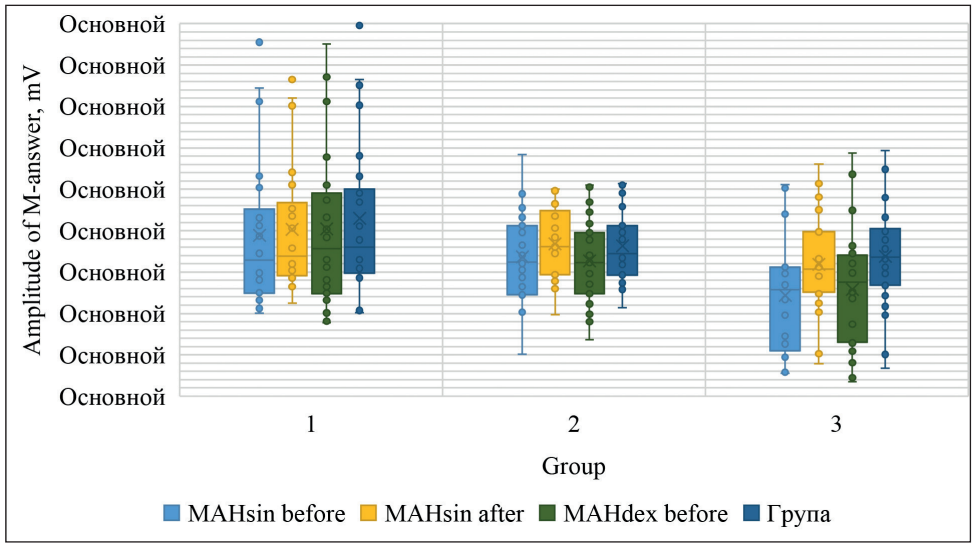

Fig 1. The amplitude of the M-response before and after the treatment with α-lipoic acid from the nerve of the muscle, which takes away the thumb of the foot.

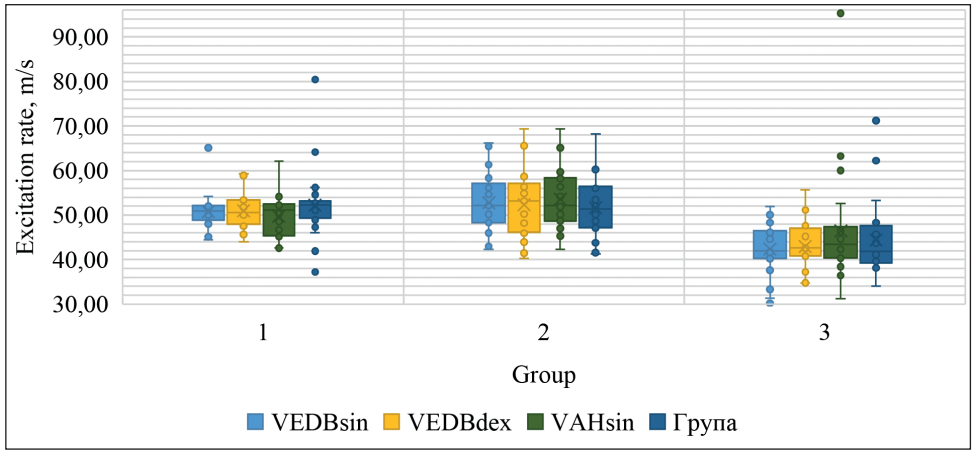

Fig 2. The speed of excitation on motor fibers before treatment with α- lipoic acid.

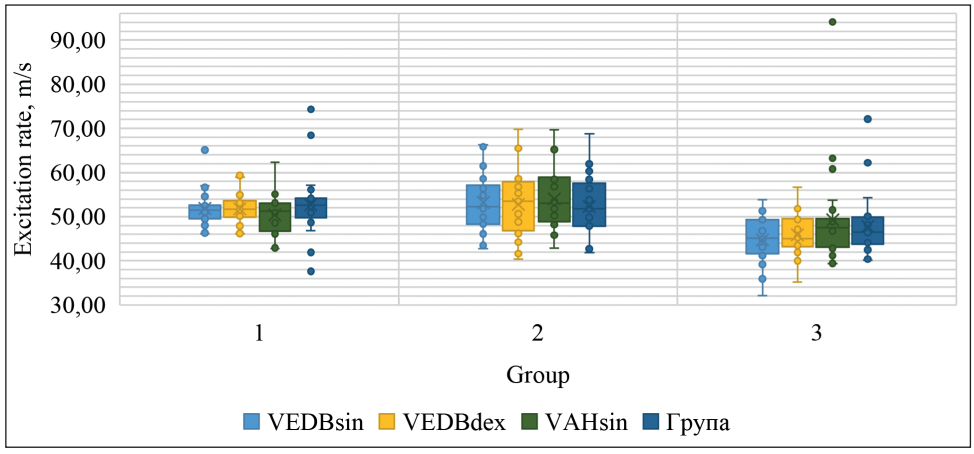

Fig 3. The speed of excitation by motor fibers after treatment with α- lipoic acid.

VAHdex - 51.32 (47.13-56.46) m/s; in group 3: VEDBsin - 42.03 (40.23-46.48) m/s , VEDBdex - 42.65 (40.8-47.0) m/s , VAHsin - 43.45 (40.38-47.4) m/s , VAHdex - 41.8 (39.23-47.65) m/s. There was a significant decrease in indicators in group 3 compared to group 1 and group 2 of VEDBsin by 17.4% and 19.4%, VEDBdex by 15.7% and 19.8% , VAHsin by 15% and 16.6% and VAHdex by 20% and 18.6%, respectively in figure 2.

The determination rate of the excitation by motor fibers after treatment revealed a decrease in the values within the normal values for all groups and their significant increase compared with the initial level, namely in group 1: VEDBsin - 51.45 (49.58-52.63) m / s, VEDBdex - 51.65 (49.85-53.58) m / s, VAHsin - 51.25 (46.72-53.1) m/s, VAHdex - 52.65 (49.73-54.13) m/s; in group 2: VEDBsin - 52.3 (47.3-57.1) m/s, VEDBdex - 53.5 (46.8-57.9) m/s, VAHsin - 53.1 (48.9-58.9) m/s, VAHdex - 51.8 (47.9 -57.6) m/s; in group 3: VEDBsin - 45.1 (41.58-49.3) m/s, VEDBdex - 45.05 (43.2-49.55) m/s, VAHsin - 47.55 (43.1-49.58) m/s, VAHdex - 46.52 (43.8-49.85) m/s. Statistically significant

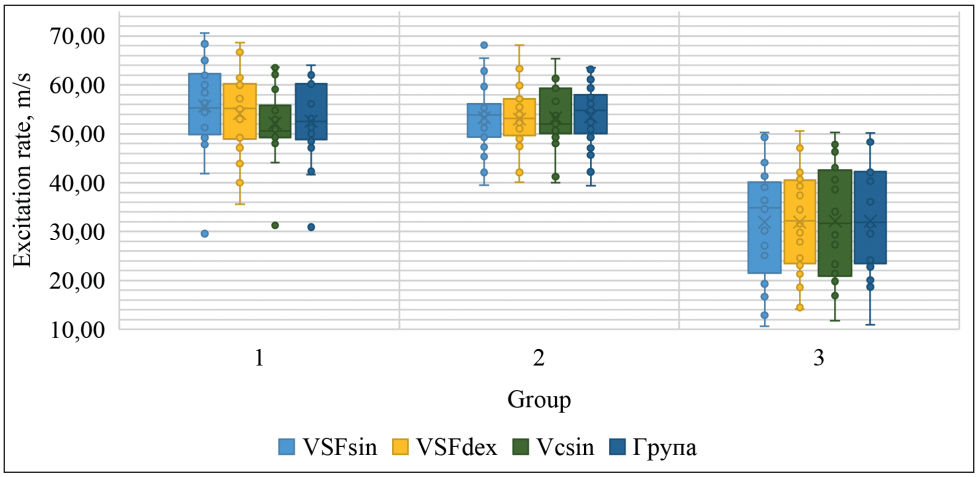

Fig 4. The rate of excitation of sensory fibers before treatment with α- lipoic acid.

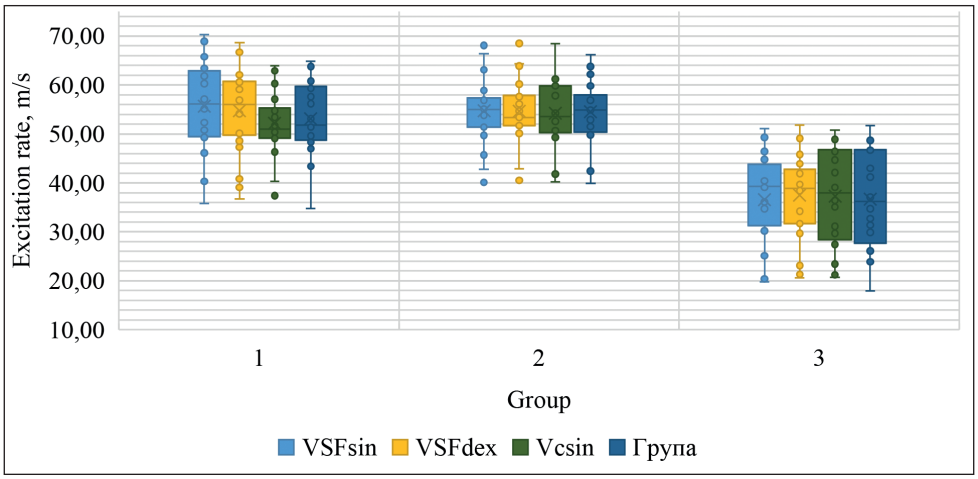

Fig 5. The speed of excitation by sensory fibers after treatment with α- lipoic acid.

differences in these indicators between groups 1 and 2 after treatment were detected, but in group 3 is revealed a decrease of VEDBsin to 17.2% and 13.8%, VEDBdex to 12.8% and 15.8% compared to groups 1 and 2, respectively, and VAHsin to 10.5% and VAHdex by 10.2% in respect to group 1, as it is shown in figure 3.

The rate of excitation of sensory fibers before treatment in groups 1 and 2 was within the mean values (50-60 m/s) and was in group 1: VSFsin - 55.63 ± 9.1 m/s, VSFdex - 54.12 ± 7.87 m/s, VCsin - 52.11 ± 6.92 m/s, VCdex - 52.55 ± 7.46 m/s, and in group 2: VSFsin - 53.34 ± 6.9 m/s, VSFdex - 52.96 ± 6.74 m/s, VCsin - 53.26 ± 5.82 m/s, VCdex - 53.47 ± 6.39 m/s. In group 3 the indicator was reduced inrelation to the norm: VSFsin - 31.96 ± 11.14 m/s, VSFdex - 31.98 ± 10.06 m/s, VCsin - 32.12 ± 11.62 m/s, VCdex - 32.17 ± 11.05 m/s. There was a significant indicators decrease in group 3 relative to group 1 VSFsin to 42.6%, VSFdex to 40.9%, VCsin to 38.4%, VCdex to 38.8%, and group 2 VSFsin to 40.1%, VSFdex to 39.6%, VCsin to 39.7%, VCdex to 39.8%, as it is shown in figure 4.

Measuring the speed of excitation rate of sensory fibers after treatment showed normal values in group 1: VSFsin - 55.65 ± 9.28 m/s, VSFdex - 54.72 ± 8.04 m/s, VCsin - 52.18 ± 6.46 m/s, VCdex - 53.14 ± 7.43 m/s; and in group 2: VSFsin - 54.77 ± 6.41 m/s, VSFdex - 54.63 ± 5.91 m/s, VCsin - 54.19 ± 6.12 m/s, VCdex - 54.53 ± 6.39 m/s; and decreased compared to the normal values in group 3: VSFsin - 36.55 ±9. 37 m/s, VSFdex - 37.53 ± 8.82 m/s, VCsin - 37.3 ± 9.84 m/s, VCdex - 36.72 ± 9.76 m/s. Statistically significant dynamics were missing among group 1, but increase of the evaluated measures was noticed in groups 2 and 3. There was revealed the reduction in group 3 relative to groups 1 and 2 respectively: VSFsin 34.3% and 33.2% , VSFdex to 31.4% and 31.3%, VCsin to 28.5% and 31.2%, VCdex to 30.9% and 32.7%, is presented in figure 5.

ENMG examination of the peripheral nerves of the lower extremities in patients with CML and CLL revealed a slight decrease in M-responses at normal values of the rate of conduction of excitation through sensory and motor fibers. In patients with MM, multiple lesions of peripheral nerve fibers of the lower extremities were detected, which is represented by a decrease in the M-response and the rate of excitation through sensory fibers and indicates deeper lesions, namely the axial cylinder, which requires longer treatment. The difference in the dynamics of the studied indicators indicates a different degree of PNP.

Administration of α-lipoic acid increased the M-response rate and the rate of excitation of motor fibers in all groups of patients. The rate of excitation through sensory fibers was improved in patients with CLL and MM. Following the use of α-lipoic acid in the complex treatment of patients with MM ENMG, the signs of peripheral nerve fiber damage in the lower extremities were worse due to the severe initial condition, but reached a medium level. The positive effect of α-lipoic acid can be caused

by a decrease in oxidative stress and endothelial dysfunction in nerve vessels, and, as a consequence, an improvement in the trophism and functional state of nerve fibers.

CONCLUSIONS

ENMG signs of defeat of PNP of the lower extremities are more expressed at MM. The appointment of α-lipoic acid in the complex treatment of PNP in patients with chronic hemoblastosis improves the functional state of the peripheral nerve fibers of the lower extremities and may be a component of pathogenetic therapy.

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The article is a fragment of the research "Clinical and pathogenetic optimization of diagnosis, prognosis, treatment and prevention of the nervous system complications disorders and neurological disorders in somatic pathology" (State registration number 0116U004190)

ORCID and contributorship:
Oleksandra O. Piddubna - 0000-0002-6468-5251 [A, B, C, D]
Nataliya V. Lytvynenko - 0000-0002-4889-3608 [B, E, F]
Anzhelina M.Krivchun - 0000-0003-2775-2029 [B, E]
Kateryna A.Taryanyk - 0000-0003-4606-5398 [B, E, F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Oleksandra O. Piddubna
Ukrainian Medical Dental Academy
23 Shevchenko St., 36000 Poltava, Ukraine
tel: +380954633153
e-mail: alexaneurolog@gmail.com

Received: 09.04.2020
Accepted: 27.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

CHARACTERISTICS OF AUTOPSY MATERIAL IN CASES OF CHRONIC DIFFUSE PATHOLOGY OF THE LIVER PARENCHYMA DIAGNOSED DURING PATIENT'S LIFETIME USING THE ULTRASOUND METHOD

DOI: 10.36740/WLek202009218

Yuliia Ya. Fedulenkova, Mykhailo S. Myroshnychenko, Olha M. Astapieva, Aleksandr A. Fatieiev, Kristina Od. Akritova, Dmytro V. Molodan
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: Of the study is to analyze autopsy cases where chronic diffuse pathology of the liver parenchyma was diagnosed during patient's lifetime using the ultrasound method.

Material and methods: In this study archival material (autopsy protocols and microspecimens of these cases) of the pathological anatomy department of the Communal Nonprofit Enterprise «Regional Clinical Hospital» (Kharkiv) was used for the period from 2012 to 2018. The cases diagnosed with a chronic diffuse pathology of the liver parenchyma according to ultrasound data were selected among all cases. Microspecimens stained with hematoxylin and eosin, picrofuxin according to van Gieson were examined using an Olympus BX-41 microscope (Japan).

The obtained digital indicators were statistically processed using the programs Statistica 6.0, Microsoft Excel 2003. To compare the parameters, parametric and nonparametric methods were used (Student's t-test, χ2 criterion, Mann-Whitney U-test). Differences were considered significant at $p<0.05$.

Results: The term «chronic diffuse pathology of the liver parenchyma», which is widely used in ultrasound diagnostics, is morphologically a collective term that combines pathological conditions such as fatty hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors of the liver, metastatic liver damage and liver infiltration by leukemic cells, liver abscesses.

According to the analysis of archival material for the period from 2012 to 2018, there was no change in the relative number of cases with fatty hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors of the liver, metastatic liver damage and liver infiltration by leukemic cells, liver abscesses. Among all cases with revealed liver pathology, both separately by year and as a whole for the entire studied period, a predominance of the relative number of cases with fatty hepatosis, fibrosis or cirrhosis of the liver was noted. The ultrasound term «chronic diffuse pathology of the liver parenchyma», taking into account the few cases identified during the analysis where the morphological picture of the liver corresponded to the age norm, needs to be improved, as well as additional diagnostic criteria should be developed in order to correctly use it in practice and avoid diagnostic errors.

Conclusions: The term «chronic diffuse pathology of the liver parenchyma», which is widely used in ultrasound diagnostics, is morphologically a collective term that combines pathological conditions such as fatty hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors of the liver, metastatic liver damage and liver infiltration by leukemic cells, liver abscesses.

The ultrasound term «chronic diffuse pathology of the liver parenchyma» needs to be improved as well as additional diagnostic criteria should be developed in order to correctly use it in practice and avoid diagnostic errors.

KEY WORDS: chronic diffuse pathology of the liver parenchyma, ultrasound method, morphological method

Wiad Lek. 2020;73(9 p. II):1999-2003

INTRODUCTION

Liver diseases are a global problem in modern healthcare system. There is a tendency toward a decrease in hepatological morbidity and mortality in a number of countries in southern and western Europe (France, Germany, Italy, Spain, etc.), while in some states of Eastern Europe these indicators are increasing (Bulgaria, Romania, the Baltic countries, etc.), and in some other countries it remains stable (the Netherlands, Poland, Scandinavian countries, etc.) [1, 2].

According to the World Health Organization there are more than 2 billion people with liver diseases in the world [3]. Ukraine has seen a significant increase in liver pathology over the past 10 years: the prevalence of chronic hepatitis has increased 2.2 times, liver cirrhosis – by 60%. The increase in the incidence of chronic liver diseases is called the «second epidemic of our century» after the «epidemic» of cardiovascular diseases [4].

Liver is characterized by a strategic location and multidimensional functions that is why it is prone to many diseases. There are over 100 known forms of liver disease caused by a variety of factors [5]. In the etiological structure of liver diseases, in addition to metabolic, autoimmune, drug-induced, toxic and genetic factors, addictions and

dependencies of modern humans – alcohol abuse, psychostimulants, eating disorders (overeating), «obesity epidemic», and the use of genetically modified organisms are becoming increasingly important against the background of an increase in prevailing hepatotropic viruses and mixed viral infections [4].

An important feature of liver diseases is their asymptomatic course in the early stages and random diagnosis during examination for other diseases (organs of the gastrointestinal tract, cardiovascular system, endocrine glands, etc.), a tendency to progression with the gradual development of liver fibrosis and cirrhosis as well as hepatocellular cancer [3].

The role of practical healthcare doctors' knowledge of the diagnostic methods for these diseases and their correct interpretation significantly increases in connection with the high levels of liver diseases prevalence. A significant role among these methods is given to ultrasound examination of the liver [6]. Here, morphological diagnostics plays a special role, i.e. biopsy or autopsy study, among diagnostic methods for studying the liver. Biopsy, according to many scientists, is the «gold standard» for the diagnosis of liver diseases. It allows us to assess the morphological and functional state of this organ, to identify pathognomonic morphological signs for a particular disease, facilitating a correct diagnosis and determining further treatment tactics for the patient [7, 8].

THE AIM

The aim of the study is to analyze autopsy cases where chronic diffuse pathology of the liver parenchyma was diagnosed during patient's lifetime using the ultrasound method.

MATERIAL AND METHODS

In this study archival material (autopsy protocols and microspecimens of these cases) of the pathological anatomy department of the Communal Nonprofit Enterprise «Regional Clinical Hospital» (Kharkiv) was used for the period from 2012 to 2018. The cases diagnosed with a chronic diffuse pathology of the liver parenchyma according to ultrasound data were selected among all cases. Microspecimens stained with hematoxylin and eosin, picrofuxin according to van Gieson were examined using an Olympus BX-41 microscope (Japan).

The obtained digital indicators were statistically processed using the programs Statistica 6.0, Microsoft Excel 2003. To compare the parameters, parametric and nonparametric methods were used (Student's t-test, $\chi 2$ criterion, Mann-Whitney U-test). Differences were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

Ultrasound examination of liver today is the most common radiological method for diagnosing the hepatobiliary system [9].

Feasibility of using ultrasound examination to diagnose chronic diffuse pathology of the liver parenchyma is determined by the following factors. The method is purely non-invasive and, when routinely performed, is not accompanied by disruption of tissue integrity, introduction of probes or contrast agents [10]. An important feature of the method is that it is safe because it is not associated with radiation exposure of the patient and uses a sufficiently low level of radiated power of ultrasound. This method has almost no contraindications; it is simple and not burdensome for the patient [11].

From the point of view of public health services organization thanks to existence of special modifications of devices (not only powerful for in-patient use, but also small-sized mobile for express diagnostics) the ultrasonic method is suitable for use at any stage and examination form of the patient (in polyclinic and hospital, field teams and specially equipped diagnostic centers, etc.) [12]. This method is characterized by a relatively low cost of equipment with an adequate cost-performance ratio in the economic aspect [11].

A relevant feature of the ultrasound method is that it gives the opportunity to simultaneously obtain information about the condition of related organs and tissues, which is especially important for patients with gastrointestinal profile because chronic diffuse pathology of the liver parenchyma is usually accompanied by comorbid pathology [13].

Among all cases of autopsies performed on the basis of the pathological anatomy department of the Communal Nonprofit Enterprise «Regional Clinical Hospital» (Kharkiv), chronic diffuse pathology of the liver parenchyma according to ultrasound examination making during patient's lifetime was found in 61 cases in 2012, accounting for 20.3 % of the total autopsies, in 2013 – in 57 cases (15.1 %), in 2014 – in 77 cases (21.7 %), in 2015 – in 64 cases (18.8 %), in 2016 – in 76 cases (21.2 %), in 2017 – in 87 cases (24.2 %), in 2018 – in 81 cases (21.1 %). During the period from 2012 to 2018 the relative number of the above cases did not change significantly ($p>0.05$).

During the analysis of autopsy protocols and microscopic examination of autopsy material it was made a conclusion and morphological diagnosis in each case (table 1). Analysis of the data in table 1 shows that the used ultrasound term «chronic diffuse pathology of the liver parenchyma» is morphologically manifested as a variety of general pathological processes in the liver, characterized for various diseases, and the liver picture corresponding to age. Thus, the ultrasound term «chronic diffuse pathology of the liver parenchyma», given the few cases where the morphological picture of the liver was normal, requires improvement and development of additional diagnostic criteria in order to properly use it in practice and avoid diagnostic errors.

The ultrasound term «chronic diffuse pathology of the liver parenchyma», as noted in table 1, was morphologically manifested by fatty hepatosis with the presence of chronic venous congestion in some cases; widespread fibrosis and formation of regenerate nodules, replacing the liver parenchyma, typical for cirrhosis; liver tumors, metastatic

Table I. Morphological analysis of chronic diffuse pathology of the liver parenchyma diagnosed by ultrasound method

Morphological diagnosis	Total number of cases for the whole period	Year						
		2012	2013	2014	2015	2016	2017	2018
	Absolute amount /%							
Fatty hepatosis or fatty hepatosis with chronic venous congestion	288/ 57.3	33/ 54.1	29/ 50.9	42/ 54.5	39/ 60.9	35/ 46.1	59/ 67.8	51/ 63.0
Fibrosis or cirrhosis of the liver	97/ 19.3	15/ 24.6	13/ 22.8	16/ 20.8	10/ 15.6	20/ 26.3	11/ 12.6	12/ 14.8
Chronic hepatitis	51/ 10.1	6/ 9.8	6/ 10.5	6/ 7.8	7/ 10.9	10/ 13.2	9/ 10.3	7/ 8.6
Malignant tumor of the liver, metastatic lesion of the liver, infiltration of the liver by leukemia cells	43/ 8.5	5/ 8.2	7/ 12.2	8/ 10.4	6/ 9.5	7/ 9.2	4/ 4.6	6/ 7.4
Liver abscesses	3/ 0.6	–	–	2/ 2.6	–	–	1/ 1.2	–
Morphological picture of the liver corresponds to the age norm	21/ 4.2	2/ 3.3	2/ 3.6	3/ 3.9	2/ 3.1	4/ 5.2	3/ 3.5	5/ 6.2

damage of the liver or liver infiltration by leukemia cells; chronic hepatitis; abscesses of the liver. The revealed liver pathology in the pathoanatomical diagnosis was the main disease or concomitant pathology. For the period from 2012 to 2018, when analyzing the dynamics of changes in the indicators of the relative number of cases with various liver pathologies, there were no ($p>0.05$) significant changes found.

In our study it has been found that among all chronic diffuse pathology of the liver parenchyma, both separately for years and for the whole studied period, a significant ($p<0.05$) number of cases occurred in fatty hepatosis, fibrosis or cirrhosis, which was also noted in the works of domestic and foreign scientists [2, 3].

Fatty hepatosis or fatty hepatosis with chronic venous congestion was found more often ($p<0.05$) in men (176 cases, 61.1 %) compared with women (112 cases, 38.9 %). The average age of those who died with the above liver pathology was 64.1±1.5 years, while the average age of men (60.8±2.1 years) was significantly ($p<0.05$) lower than the average age of women (66.8±1.9 years).

In most cases it was possible to identify the cause of fatty hepatosis development when analyzing anamnestic data. So, in 179 cases (62.2 %) the cause of fatty hepatosis development was hypoxia caused by chronic pathology of the cardiovascular and respiratory systems. Endocrine and metabolic disorders (diabetes, obesity, etc.) caused the development of fatty hepatosis in 51 cases (17.7 %). In 46 cases (16.0 %) the cause of fatty hepatosis development was toxic effects due to alcohol abuse, chemotherapy in patients with malignant tumors of various localizations. It was not possible to identify its genesis in 12 cases (4.1 %).

Macroscopically the liver in fatty hepatosis was characterized by a smooth surface. The liver capsule was thin, transparent, smooth and shiny. In 263 cases (91.3 %) the liver had a dense texture and in 25 cases (8.7 %) it was flabby. In 199 cases (69.1 %) the liver on the cross section looked like nutmeg due to the presence of red, dark red, yellow and brown-yellow areas, and in 89 cases (30.9 %) it was yellow or gray-yellow.

«The nutmeg liver» was microscopically characterized by a sharp dilation and hyperemia of the central veins and adjacent inter-beam capillaries, presence of diapedetic hemorrhages and deposition of the hemosiderin pigment. On the periphery of the hepatic lobules small-droplet and large-droplet fatty degeneration of hepatocytes was determined, as a result of which the latter lost their inherent shape and beam-like arrangement, acquired a rounded shape. In 15 cases (5.2 %) there was a discompletion of hepatocytes with the presence of vacuole dystrophy, polymorphic cell infiltration of varying severity and necrosis of individual cell groups. Inflammatory changes were accompanied by a fibrosing reaction expressed to varying degrees. Hereby, portal, periportal, perivenular and perisinusoidal fibrosis was noted in some places with the formation of fibrotic septa.

In 89 cases (30.9 %) where macroscopically the liver on the cross section was yellow or gray-yellow in color scanning microscopy revealed pulverized, small-droplet, medium-droplet and in some fields of view large-droplet obesity of hepatocytes. Fatty infiltration encompassed single hepatocytes, groups of hepatocytes or the entire liver parenchyma. Fusion of fat-filled hepatocytes with the formation of fatty cysts was noted in some fields of view. It should be noted that hepatocytes with signs of fatty degeneration in part of the visual fields were localized mainly around the portal tracts, central veins and in part of the visual fields did not have any connection with the anatomical structures of the liver.

Fibrosis or cirrhosis was noted significantly ($p<0.05$) more often in men (72 cases, 74.2 %) compared with wom-

en (25 cases, 25.8 %). The average age of the deceased with the above pathology was 56.5±1.9 years. The average age of men (51.8±1.5 years) was significantly ($p<0.05$) lower than the average age of women (62.2±2.2 years).

Analyzing the clinical and anamnestic data, it has been found that the cause of liver fibrosis or cirrhosis development in 49 cases (50.5 %) was the toxic effect of alcohol, in 21 cases (21.6 %) – a chronic pathology of the cardiovascular system, which resulted in the formation of congestive or nutmeg cirrhosis of the liver, in 10 cases (10.3 %) – a viral hepatitis in anamnesis. In 9 cases (9.4 %) fibrosis or cirrhosis of the liver developed as a result of immune disorders, i.e. had an autoimmune genesis. Genesis of the above liver pathology development could not be established in 8 cases (8.2 %).

Macroscopically the liver in fibrosis or cirrhosis was reduced in size, of dense texture, diffusely deformed by numerous nodules (size from 0.3 to 0.5 cm). It was revealed on the cross section the separation of liver tissue into rounded nodules bounded by fibrous bands and rings. The color of the nodules ranged from pale brown, greenish yellow to dark red.

Massive fibrous septa, dissecting the organ parenchyma, or the formation of portal cirrhosis with powerful connective tissue septa between the false hepatic lobules were observed during the microscopical examination. Portal tracts were sharply expanded with sclerotic stroma and vessels. Moderate, sometimes abundant lymphohistiocytic infiltration was noted in septum and portal tracts. Hepatocytes of false lobules were noticed in some areas with focal or diffuse small-droplet, large-droplet fatty degeneration. Hydropic degeneration of hepatocytes was determined in some fields of view, while in others – necrotic changes of liver cells. There was an increase in the number of small ductal elements, indicating proliferative processes in the bile ducts. Monolobular cirrhosis was predominant among all types of cirrhosis of the liver when the regenerative nodes were built on the basis of one fragmented lobule over the multilobular one, also when the fragments of several lobules were included in the composition of the regenerative nodes. Monomultilobular cirrhosis was not detected.

A significant ($p<0.05$) prevalence of liver fibrosis and cirrhosis, liver hepatosis in men compared with women was noted in Ukraine, according to the State Statistics Service of Ukraine, when analyzing the gender characteristics of liver pathology [14].

Chronic hepatitis was significantly ($p<0.05$) more often found in men (39 cases, 76.5 %) compared with women (12 cases, 23.5 %). The average age of those who died with this pathology was 43.3±1.5 years. The average age was significantly ($p<0.05$) lower in men (41.5±1.6 years) than in women (45.0±1.1 years).

The results of the clinical and anamnestic analysis revealed the cause of the chronic hepatitis development. Hence, in 36 cases (70.6 %) infectious genesis of chronic hepatitis was found, in 12 cases (23.5 %) chronic hepatitis occurred as a result of toxic effects (alcohol intoxication), in 3 cases (5.9 %) metabolic disorders were the cause.

Macroscopically, the liver was of normal size, the capsule was diffusely thickened, whitish or whitish-gray in color. Liver tissue was dense, in some cases flabby. On the cross section the liver was greyish-brown or brown-yellow. Microscopically chronic persistent hepatitis was revealed in 34 cases (66.7 %), in 12 cases (23.5 %) – chronic active hepatitis, in 5 cases (9.8 %) – chronic cholestatic hepatitis.

Malignant liver tumors, metastatic liver lesion or liver infiltration by leukemia cells were significantly more common in men (31 cases, 72.1 %) compared with women (12 cases, 27.9 %). The average age of the deceased with the above pathology was 46.4±1.5 years. The average age of men (46.5±1.6 years) did not significantly differ ($p>0.05$) from the average age of women (46.3±1.7 years).

Macroscopically in cases of leukemic cell infiltration, the liver was enlarged and dense, characterized by a smooth surface, a thin and transparent capsule, greyish-brown, brown or grayish-yellow color on the cross section. In cases of malignant neoplasm or metastatic tumor lesion the surface of the liver was finely tuberous in some places, coarsely tuberous in other places, the lower edge was rounded, the tissue was flabby, dark red, sometimes blackish, sometimes grayish-yellow color with alternating dense nodular formations.

Microscopic examination of the liver in 22 cases (51.2 %) showed marked diffuse proliferation of leukemic cells of the myeloid series along sinusoids and in portal tracts; diffuse fatty degeneration of hepatocytes; hyperemia of portal vessels with plasmostasis, desquamation of the endothelium and paravasal hemorrhage. In 16 cases (37.2 %) it was found a metastatic liver damage because of the development cancer of various localization (bronchus, stomach, colon, pancreas, mammary glands) and skin melanoma. Hepatocellular liver cancer was diagnosed in 3 cases (6.9 %) and cholangiocellular cancer – in 2 cases (4.7 %).

Liver abscesses were found in 3 men, whose average age was 42.6±1.5 years. Clinical and anamnestic analysis, the results of macroscopic examination made it possible to interpret these abscesses as cholangiogenic. Macroscopically the size of the liver, the consistency and the color on the cross section were not changed. A few cavity formations of a round-oval shape with a diameter of 0.5 to 1.5 cm were found in the area of the gallbladder bed in the liver, containing a mucous mass of yellowish-greenish color in the lumen. Survey microscopy revealed acute liver abscesses.

CONCLUSIONS

1. The term «chronic diffuse pathology of the liver parenchyma», which is widely used in ultrasound diagnostics, is morphologically a collective term that combines pathological conditions such as fatty hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors of the liver, metastatic liver damage and liver infiltration by leukemic cells, liver abscesses.
2. According to the analysis of archival material for the period from 2012 to 2018, there was no change in the relative number of cases with fatty hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors

of the liver, metastatic liver damage and liver infiltration by leukemic cells, liver abscesses. Among all cases with revealed liver pathology, both separately by year and as a whole for the entire studied period, a predominance of the relative number of cases with fatty hepatosis, fibrosis or cirrhosis of the liver was noted.

3. The ultrasound term «chronic diffuse pathology of the liver parenchyma», taking into account the few cases identified during the analysis where the morphological picture of the liver corresponded to the age norm, needs to be improved, as well as additional diagnostic criteria should be developed in order to correctly use it in practice and avoid diagnostic errors.
4. Hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis, malignant tumors of the liver, metastatic damage of the liver, infiltration of the liver by leukemia cells, liver abscesses develop more often in men. When analyzing the age-related features of the revealed liver pathology, it has been noted that at an earlier age patients develop liver abscesses (average age – 42.6±1.5 years), chronic hepatitis (average age – 43.3±1.5 years), malignant tumors of the liver, metastatic liver damage, liver infiltration by leukemia cells (average age – 46.4±1.5 years), and at a later age – fibrosis or cirrhosis (average age – 56.5±1.9 years), hepatosis of the liver (average age – 64.1±1.5 years). Chronic hepatosis, fibrosis or cirrhosis of the liver, chronic hepatitis in men develops at an earlier age than in women.

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ORCID and contributionship:

Yuliia Ya. Fedulenkova: 0000-0001-8599-9500 [A, D, F]
Mykhailo S. Myroshnychenko: 0000-0002-6920-8374 [A, D, E]
Olha M.Astapieva: 0000-0003-1136-6131 [B, E]
Aleksandr A. Fatieiev: 0000-0003-1350-8623 [C, F]
Kristina Od. Akritova: 0000-0001-5231-523X [B, C]
Dmytro V. Molodan: 0000-0002-7679-828 [B, E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Mykhailo S. Myroshnychenko
Kharkiv National Medical University
27A Svetlaya str., apt. 70, 61129 Kharkiv, Ukraine
tel: +380501699763, +380961033038
e-mail: msmyroshnychenko@ukr.net

Received: 17.04.2020
Accepted: 30.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

HYGIENIC SUBSTANTIATION OF NECESSITY FOR MONITORING IN THE ENVIRONMENTAL OBJECTS OF SDHI FUNGICIDES CONSIDERING THEIR POSSIBLE IMPACT ON THE THYROID GLAND

DOI: 10.36740/WLek202009219

Anna M. Antonenko[1], Bohdan I. Shpak[2], Olena P. Vavrinevych[1], Sergii T. Omelchuk[1], Tetiana I. Zinchenko[1]
[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]DEPARTMENT OF REGISTRATION AND REGULATION OF «SYNGENTA» LLC, KYIV, UKRAINE

ABSTRACT

The aim: Was hygienic substantiation of necessity for monitoring in the environmental objects of SDHI fungicides considering their possible impact on the thyroid gland.

Materials and methods: To test the proposed selection criteria for hygienic monitoring of pesticides that affect the thyroid gland, we evaluated 4 new SDHI fungicides from the chemical class of pyrazolecarboxamides (isopyrazam, pentiopyrad, sedaxan, fluxapyroxad).

Results: Based on the results obtained, all studied compounds are assigned to the second pesticide group, hygienic monitoring of which is desirable but not required. This is due, on the one hand, to their low toxicity, to the other, to low environmental sustainability.

Conclusions: It was shown, that compared to other classes of pesticides, the studied are much less dangerous in terms of groundwater contamination.

KEYWORDS: fungicides, selection criteria, hazard class, thyroid gland, monitoring

Wiad Lek. 2020;73(9 p. II):2005-2008

INTRODUCTION

Despite their popularity and widespread use, pesticides pose a serious risk to human health not only when mixing and applying pesticides or working in cultivated fields, but in the consumption of food and water containing pesticide residues [1, 2]. The risk assessment for the population when consuming food containing pesticide residues is mandatory in the US and European countries [3, 4]. In Ukraine, when conducting state tests of new pesticide formulations, a risk assessment is carried out only for agricultural workers and taking into account just possible inhalation and skin contact with pesticide compounds.

In the countries of the European Union and the USA, risk assessment techniques for non-professional contingents have long been tried and actively used [3-7]. Recommendations for such monitoring have also been developed in Ukraine in recent years [8]. The vast majority of such monitoring models existing in Ukraine and in the world do not include assessment of specific indicators for pesticides that may affect the thyroid gland.

Given the level of endocrine pathology in the world, and in particular the prevalence of thyroid disease [8-11], the introduction of such techniques is relevant, timely and necessary.

THE AIM

The purpose was hygienic substantiation of necessity for monitoring in the environmental objects of fungicides – succinate-dehydrogenase inhibitors (SDHI), considering their possible impact on the thyroid gland.

MATERIALS AND METHODS

Before, we have improved the pesticide monitoring system [8], considering their possible effect on the functioning of the thyroid gland [12], namely:

1. A point evaluation of the selection criteria for monitoring studies was proposed;
2. Additional (groundwater and surface water contamination index (LEACH), integral pesticide contaminated water consumption hazard index (IPCWCI), integral pesticide contaminated food consumption hazard index (IPCFCI) were proposed;
3. Specific criteria (influence on thyroid gland as target organ, severity of pesticide induced tyrosinemia (plasma tyrosine level, nmol / ml)).

After adding all points received, the need for monitoring is evaluated as follows: for a total of 11-16 points – monitoring is not required; 17-27 points – monitoring is desirable; 28-38 – mandatory monitoring; 39-44 – pesticide application should be prohibited [12].

To test the proposed selection criteria for hygienic monitoring of pesticides that affect the thyroid gland, we evaluated 4 new SDHI fungicides from the chemical class of pyrazolecarboxamides (isopyrazam, pentiopyrad, sedaxan, fluxapyroxad).

RESULTS AND DISCUSSION

Environmental monitoring models that exist in Ukraine today [8, 13] provide for observations of the state of the

Table I. Selection of investigated fungicides for hygienic monitoring

Criteria	Index value (score in points)			
	isopyrazam	pentiopyrad	sedaxan	fluxapyroxad
Allowable daily dose (ADD), mg/kg	0,01 (2)	0,1 (1)	0,1 (1)	0,02 (2)
Class of hazard according to State Standards 8.8.1.002-98	2 (3)	3 (2)	3 (2)	3 (2)
Impact on the thyroid gland as a target organ	weak effect in animal experiments (2)	weak effect in animal experiments (2)	weak effect in animal experiments (2)	weak effect in animal experiments (2)
The severity of pesticide-induced tyrosinemia (plasma tyrosine levels, nmol/ml)	<300 (1)	<300 (1)	<300 (1)	<300 (1)
Half-life period (DT_{50}) in soil, day	12,5 (2)	3,0 (1)	12,5 (2)	11,3 (2)
Half-life period (DT_{50}) in water, day	2,3 (1)	9,9 (2)	14,0 (3)	4,4 (1)
Half-life period (DT_{50}) in plants, day	3,6 (1)	2,5 (1)	2,8 (1)	3,8 (1)
the Groundwater and Surface Water Pollution Index (LEACH), units	0,0028 (1)	0,0214 (2)	0,0342 (2)	0,0534 (3)
Screening of maximum pesticide concentration in groundwater (SCI-GROW), μg/l	$5,5\times10^{-3}$ (2)	$5,4\times10^{-3}$ (2)	$3,4\times10^{-2}$ (2)	$2,6\times10^{-3}$ (2)
Integral index of contaminated water consumption hazard (IICWCH), points	4 (1)	5 (2)	6 (2)	5 (2)
Integral index of contaminated food consumption hazard (IICFCH), points	7 (3)	6 (2)	8 (3)	8 (3)
Total score	19	18	22	21

environment (air, land waters, coastal waters, soil), and the level of pollution. The implementation of these functions is entrusted to the Ministry of Energy and Environmental Protection and other central executive organizations, which are the subjects of the state environmental monitoring system, as well as to the enterprises, institutions and organizations whose activities lead to or may worsen the environment [13].

Our monitoring system model proposes a risk assessment for non-professional contingents whose organisms can be exposed with pesticides mainly by oral intake with drinking water and food. In addition, it lays down specific criteria for pesticide monitoring that affect the thyroid gland, which is extremely relevant today for many countries in the world [10-11].

Such hygienic monitoring of pesticides that affect the thyroid gland requires, first of all, areas with intensive agriculture. In Ukraine, for example, such regions as Vinnytsia, Cherkasy, Poltava, Kherson, Odessa, Mykolaiv. However, in other areas such monitoring is desirable, as chemical plant protection products are being actively introduced into world agriculture, including privately owned farms that are mostly uncontrolled, which complicates the determination of pesticide application volumes in them.

According to the toxicological criteria, all tested compounds are low- and moderately toxic: relatively high allowable daily doses, 2-3 hazard class.

In soil and climatic conditions of Eastern, Southern and partly Central Europe, including Ukraine, the investigated fungicides are unstable in environmental objects and agricultural raw materials [14, 15].

It was established that in soil-climatic conditions of Ukraine the risk of groundwater contamination by all investigated fungicides (isopyrazam, pentiopyrad, sedaxan, fluxapyroxad) is low, and their maximum possible concentrations in groundwater are insignificant and much lower than allowable. This is due to the low percentage of active ingredients in the fungicide formulations and indicates the relative safety for human health of drinking of water in which the test compounds may be present [14].

Given that, isopyrazam, pentiopyrad, sedaxan, fluxapyroxad based formulations are used predominantly for the treatment of cereals (consumed after purification and heat treatment), the risk to humans of consuming contaminated products is also relatively low [16].

Each of proposed criteria was evaluated according to the proposed scale in points and their sum was calculated (Table I).

Given that, isopyrazam, pentiopyrad, sedaxan, fluxapyroxad based formulations are used predominantly for the treatment of cereals (consumed after purification and heat treatment), the risk to humans of consuming contaminated products is also relatively low [16].

Compared to other classes of pesticides, the studied are much less dangerous in terms of groundwater contamination. For example, herbicides that have been successfully used in Ukrainian and world agriculture for many years, benzoic acid derivative – dicamba, sulphonyl urea – nicosulfuron, and strobilurin class fungicide – azoxystrobin are characterized by high risk of groundwater contamination [17, 18]. Similarly, pymetrozine is a fungicide that belongs to a relatively new chemical class of fungicides, namely pyridine azomethrines [17].

There may be several reasons. For example, low toxicity, low environmental stabilityю Fungicides from the studied classes do not lead to the development of tyrosinemia. This effect is observed in the herbicides of 4-hydroxyphenylpyruvate dioxygenase inhibitors and the tetramic and tetronic acid-like insecticides [19, 20].

CONCLUSIONS

Based on the results obtained, all studied compounds are assigned to the second pesticide group, hygienic monitoring of which is desirable but not required. This is due, on the one hand, to their low toxicity, to the other, to low environmental sustainability.

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ORCID and contributionship:

Anna M. Antonenko: 0000-0001-9665-0646 [A, D]
Bohdan I. Shpak: 0000-0001-9273-8544 [B]
Olena P. Vavrinevych: 0000-0002-4871-0840 [E]
Sergii S. Omelchuk: 0000-0003-3678-4241 [F]
Tetiana I. Zinchenko: 0000-0002-3541-9480 [C]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Anna M. Antonenko
Bogomolets National Medical University
13 Tarasa Shevchenko st., 01601Kyiv, Ukraine
tel:+380991466331
e-mail: antonenko1985@ukr.net

Received: 09.03.2020
Accepted: 24.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

ESTIMATION OF RELATIVE RISK OF DEVELOPMENT AND INFORMATIVENESS OF DIAGNOSTIC METHODS OF HYPERPROLIFERATIVE PROCESSES OF ENDOMETRIUM

DOI: 10.36740/WLek202009220

Alla V. Boychuk[1], Tetiana V. Vereshchahina[1], Iryna M. Nikitina[2]
[1]TERNOPIL STATE MEDICAL UNIVERSITY NAMED AFTER I. YA. GORBACHEVSKY, TERNOPIL, UKRAINE
[2]SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

The aim: Of the study was to conduct a comparative analysis of the results of ultrasound and hysteroscopic examinations, followed by histopathological findings to study the diversity and characteristics of clinical and anamnestic manifestations of the hyperproliferative pathology of endometrium, which can be used to form risk groups for the occurrence of this pathology. Analysis of the informativity of ultrasound and hysteroscopy allows us to evaluate the advantages of hysteroscopy, however, it does not exclude the high efficiency of ultrasound, defining these two diagnostic methods as complementary.

Materials and methods: We studied 119 medical records of patients of the Gynecological Department of Minipal Non-Commercial Enterprise "Ternopil Municipal City Hospital No. 2", who applied for medical assistance because of benign endometrial hyperplasia in the reproductive age with a verified diagnosis of "uterine polyp" during 2017–2018. The control group consisted of 30 patients of the same age group, with menstrual disorders with no signs of hyperplastic processes of endometrium. With the consent of the patients, they were treated with diagnostic hysteroscopy in order to study evacuated material from the uterus. The results of the histological study confirmed the absence of signs of hyperplastic processes of endometrium. The results of diagnostic methods were evaluated by comparing the material's histological data with the results of ultrasound and hysteroresectoscopy.

Results: Taking into account the results of our research, women with hyperplastic processes of endometrium have the risk of the pathology of the nervous system is in 2.71 times higher (OR=2.71, CI–0.88: 8.33), cardiovascular pathology—in 2.04 (OR=2.04, CI–0.57:7.34), vascular diseases of the lower extremities—in 1.81 times (OR=1.81, CI–0.21:15.32) compared with the control group. While the risk of pathology of the urinary system and organs of vision is only—OR=0.48, CI–0.11:2.03 and OR=0.75, CI–0.08:7.48, respectively. Analyzing the results of the study using ultrasound examination, it was found that endometrial polyposis in combination with uterine leiomyoma was not detected in 3 women (15%), while all the results of hysteroscopy were confirmed by histopathological studies. When the endometrial hyperplastic processes were combined with adenomyosis—according to ultrasound examination a false positive result was obtained in 2 patients (13.3%), and in a hysteroscopic study we determined –1 false positive result.
In patients the diagnosis of "endometrial polyp" according to the results of hysteroscopy was not confirmed in 2 women (2 false positive results 2.99%) and in 5 cases of ultrasound examination (5 false negative results 7.46%). The use of ultrasound examinations in patients with endometrial hyperplastic changes, according to our data, made it possible to identify pathology in 88.39% of cases, while the information content of the hysteroscopy was 98.21% ($p<0.001$).

Conclusions: Thus, the results of the subjective examination of patients in the gynecological department: complaints, anamnestic data on gynecological and extragenital pathology should be used to identify etiopathogenetic factors and the formation of risk groups for the occurrence of hyperplastic processes of endometrium. Women with cervical erosion, uterine myoma and episodes of herpetic rash on the mucous membranes in past medical history have a higher likelihood of hyperplastic processes of endometrium.
The vast majority of patients (63.87%) with polyps of the body of the uterus have a combined hyperproliferative pathology, which requires an individual approach to planning the scope of diagnostic examination and the choice of treatment method. Visualization of endometrium with hysteroscopy is more informative than ultrasound for diagnosing hyperproliferative processes, including uterine polyps. Hysteroscopic polypectomy has a high level of both clinical and economic benefits as well as diagnostic value in patients with hyperplastic processes of endometrium.

KEY WORDS: hyperproliferative pathology, hyperplastic processes of endometrium, hysteroscopic examinations

Wiad Lek. 2020;73(9 p. II):2011-2016

INTRODUCTION

The problem of hyperplastic processes of endometrium (HPE) occupies one of the main places in gynecological practice and constitutes (according to various sources) from 17% to 59% of the total gynecological pathology [10, 11]. The interest in improving the diagnosis and treatment of benign hyperproliferative lesions of the uterus is not only necessary and expedient from the standpoint of oncological alertness, but also given the frequent recurrences of pathological changes, reproductive disorders in this category of women, disorders of the ovarian-menstrual cycle and the development of chronic anemia.

Diagnostics of the endometrial polyps (EP) does not cause any particular difficulties and has a clear algorithm of actions: visualization of formation, its evacuation followed by histopathological studies (HS) to optimize the further tactics of the patient management [2]. At the same time, the curettage of the uterus and a "blind" biopsy are

not the methods of choice today for diagnosing polyps of the uterus. When using this method, there is a risk of fragmentation of the polyp tissue, which often complicates the work of the histologist [3].

Today, the direct endoscopic visualization of the endometrial cavity (hysteroscopy) is considered the "gold standard" in the diagnosis and treatment of polyps of the uterus body, and hysteroscopic polypectomy [4-6], which is deservedly called as "See–and–Treat" method [7]. Nowadays, the method of hysteroscopy is widely used in many countries of the world, it is included in the standards of examination and treatment of patients with various gynecological pathologies. Analysis of the diagnostic value (sensitivity and specificity) of this method of examination and treatment of patients with various pathologies of the female reproductive system confirmed not only the diagnostic sensitivity, but also the economic feasibility of using hysteroscopy [1, 9].

In particular, the meta–analytical study that analyzed the hysteroscopic data of the main pathological changes in the endometrium in women with blood secretions from the genital tracts (based on Medline and the Cochrane Library data) revealed a high diagnostic accuracy of hysteroscopy for endometrial cancer, endometrial polyp and submucous leiomyoma [8].

Considering the above, to study the diversity of the clinical presentation of hyperproliferative pathology, we have analyzed and summarized the clinical and anamnestic data, parity, considered the accompanying pathology, and also analyzed the results of ultrasound and hysteroscopic examinations with further histopathological findings.

THE AIM

The aim to conduct a comparative analysis of the results of ultrasound and hysteroscopic examinations with further histopathological findings and the clinical and anamnestic features of patients with hyperproliferative pathology in order to determine the etiopathogenetic mechanisms of the development of endometrial pathological processes.

MATERIALS AND METHODS

We studied 119 medical records of patients of the Gynecological Department of Minipal Non-Commercial Enterprise "Ternopil Municipal City Hospital No. 2", who applied for medical assistance because of benign endometrial hyperplasia in the reproductive age with a verified diagnosis of "uterine polyp" during 2017–2018. The age of women ranged from 20 to 49 years (on average 34.52 ± 2.51). The research group included patients with simple and complex non-atypical endometrial hyperplasia according to the classification of hyperproliferative processes of endometrium (developed by the Subcommittee on Uterine Corpus of the International Society of Gynecologists and Pathologists and approved by WHO, 1994). According to its data, hyperplastic processes of endometrium are divided into 5 groups:

- simple non-atypical endometrial hyperplasia;
- complex non-atypical endometrial hyperplasia;
- simple atypical endometrial hyperplasia;
- complex atypical endometrial hyperplasia;
- adenocarcinoma

The study group did not include medical records of women with alimentary–constitutional obesity (BMI>30.0).

The control group consisted of 30 patients of the same age group, with menstrual disorders with no signs of HPE. With the consent of the patients, they were treated with diagnostic hysteroscopy in order to study evacuated material from the uterus. The results of the histological study confirmed the absence of signs of HPE.

Ultrasound examination (US) was carried out on the device "Philips HD11 XE" with a 3.5 MHz convex sensor and a 7.5 MHz vaginal sensor. Sonographic studies were conducted in the proliferative (6–8 day) or secretory (20–22 day) phases of the menstrual cycle.

Hysteroscopy was performed in the operative room with intravenous anesthesia on hard fiber optics of Companies "KARL STORZ" from the 6th to the 11th day of the menstrual cycle (with the menstrual cycle preserved). Taking into account the results of ultrasound and hysteroscopy data, a resectoscope was used to completely remove the hyperplastic cells of the uterus and the cervical canal with further follow-up examination. After complete removal of the pathologically altered endometrial tissue, the resulting material was sent for histological examination. The material was fixed in 10% buffered formalin solution. Histological examination of tissues was performed by the standard method of serial sections (paraffin sections were stained with hematoxylin–eosin and according to Van Gieson). The findings on the histological types of hyperplasia and endometrial polyps were based on the WHO classification for endometrial pathology (2014).

The results of diagnostic methods were evaluated by comparing the material's histological data with the results of ultrasound and hysteroresectoscopy.

All diagnostic and therapeutic manipulations were carried out after the written consent of the patients for examination and treatment in accordance with the protocol approved by the Committee on Bioethics (No. 53/June 03, 2019). Consent for surgical treatment was obtained prior to treatment.

The obtained data was processed using standard statistical methods using HP PREMIER EXPERIENCE personal computer with program Microsoft Word 2010, the graphics were built using Microsoft Excel. Statistical processing was carried out by the program Statistika 10. For statistical processing, the qualitative and quantitative variables were determined. For qualitative data, a frequency analysis of the occurrence of signs was performed with the determination of the error of the mid and 95% confidence interval. The quantitative variables were checked for normal distribution using descriptive statistics of criteria of Kolmogorov–Smirnov. For risk assessment there were determined the odds ratio, confidence intervals, relative risk, etiological factor of influence, absolute (directly associated risk), percentage of associated risk and population risk.

Table I. Relative risk of complaints in patients with hyperplastic processes of endometrium

No.	Complaints	OR	Confidence interval	
			lower bound	upper bound
1	disorder of the menstrual cycle	0,8	0,34	1,88
2	Pain	2,39	0,67	8,53
3	frequent and significant menstruation	1,31	0,41	4,18
4	Infertility	0,66	0,20	2,25
5	general weakness	1,01	0,10	9,40
6	combination of women's complaints	1,5	0,41	5,50
7	without significant complaints	0,36	0,11	1,19
Level of significance λ (alpha)=0.05				

Table II. The relative risk of hyperplastic processes of endometrium in patients with concomitant gynecological pathology

No.	Gynecological anamnesis	OR	Confidence interval	
			lower bound	upper bound
1	erosion of the cervix	5,71	2,17	15,02
2	ovarian cysts	2,95	0,37	23,83
3	chronic inflammatory diseases of the uterine appendages	3,29	1,07	10,08
4	ectopic pregnancy	0,50	0,04	5,66
5	mammary pathology	1,43	0,30	6,81
6	polyps of the cervical canal	1,01	0,11	9,37
7	myoma of the uterus	6,21	0,8	48,19
8	herpetic rash on mucous membranes	5,05	1,66	15,36
9	combined pathology	9,8	2,23	43,06
Level of significance λ (alpha) = 0.05				

RESULTS

Analysis of the results of the subjective examination showed that the most frequent complaints when admission to hospital in patients with endometrial hyperproliferative processes were menstrual disorders—(27 women—28.57%), pain (25 patients—21.01 %%), frequent and significant menstruation (20 patients— 16.81%), infertility in 11 cases (9.24%), 4 women felt general weakness (3.36%), a combination of complaints was found in 17 cases (14.29%), without special complaints were 8 women (6.72%) (p=0.01). The relative risk (RR) –OR was calculated—the occurrence of these complaints at admission to hospital of patients with HPE compared with the control group. The above data are shown in table I.

The maximum duration of this disease was 15 years, the minimum—2 weeks.

Fourty-forty patients (36.97%) received prior treatment for HPE: 10 women (8.40%) were prescribed hormone therapy, in 5 cases (4.20%) was used anti-inflammatory therapy. Firty percent of patients indicated on fractional therapeutic and diagnostic curettage (FTDC) in the past medical history: 17 women—once (14.29%), 5—two or more times (4.2%). Hormone therapy after FTDC received 7 patients (22.73%) (p <0.005).

Assessment of the relative risk of HPE taking into account the peculiarities of the gynecological past medical history. The above data are shown in table II.

When specifying the gynecological past medical history, cervical erosion was found in 70 women (62.2%), 40 patients (35.5%) suffered from chronic inflammatory diseases of the uterine appendages, 21 women (18.4%) reported uterine myoma, ovarian cysts were diagnosed in 11 patients (9.6%), 4 women (3.8%) noted polyps of the cervical canal in their past medical history, 2 women (1.8%) had ectopic pregnancies. Breast pathology was documented in 11 medical records (9.6%), in addition there were periodic herpetic rash on the mucous membranes—52 (43.70%) (p <0.005). Combined pathology was observed in 49 women (41.18%).

A detailed study of reproductive function showed that 22 women had 1 birth in their past medical history (18.49%), 32 gave birth 2 times or more (26.89%). Women who did not give birth amounted 48.74% (58 patients). Twenty-six and six hundredths percent of patients had abortions in their anamnesis, among them 1 abortion—16 women (13.45%), 2 or more—15 (12.61%), and 81 women had no abortions in their anamnesis (68.07%). For the purpose of contraception, 19 patients (11.9%) had IUDs, 9 patients used hormonal contraceptives (7.56%) (p <0.005).

An extragenital pathology was detected in 74 patients (64.18%), of which 25.21% was combined (p<0.005). The structure of associated diseases revealed: changes in the cardiovascular system in 18.49% of patients, diseases of the nervous system in 29.41%, pathology of the gastroin-

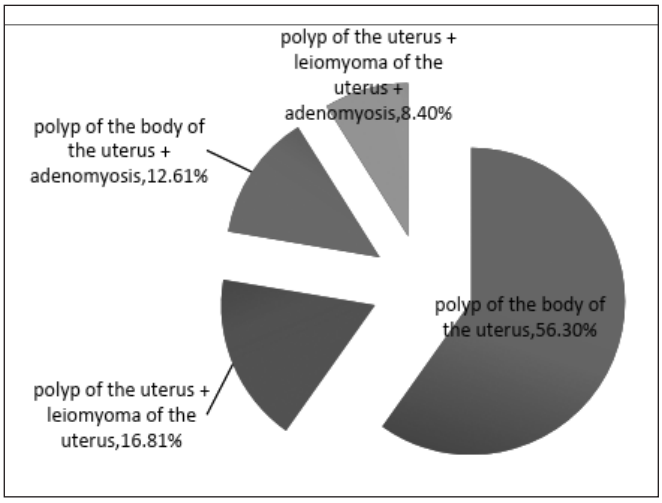

Fig 1. Structure of hyperproliferative pathology of myometrium and endometrium

testinal tract—15.97%, diseases of the urinary–excretory system—5.04%, respiratory systems—8.40%, endocrinopathy— 29.41%, varicose disease of the lower extremities—5.88%, ophthalmic pathology— 2.52%.

A comparative analysis of the presence of extragenital pathology with the risk assessment in women with HPE in different systems of the body was conducted. The above data are shown in table III.

According to the results of the conducted clinical laboratory research, the most commonly diagnosed isolated pathology of endometrium was a polyp (56.30), while in 31 women (26.05%) polyps were detected not only in the uterine cavity, but also in the cervical canal. In 20 cases (16.81%), the uterine polyp was combined with hyperproliferative uterine disease—leiomyoma. The combination of the uterine polyp with adenomyosis was detected in 15 patients (12.61%). A leiomyoma with adenomyosis was diagnosed with the uterine polyp in 10 patients (8.40%).

During the study of the structure of hyperproliferative pathology in these patients there was revealed a combined pathology of myo- and endometrium. The above data are shown in Figure 1.

A comparative assessment of the informativeness of ultrasound and hysteroscopy with the final results of a histopathological study in the diagnosis of endometrial hyperplasia was carried out. The above data are shown in table IV.

The analysis of the results of subjective examination of patients with HPE showed frequent pain syndrome in comparison with the control group in 2.71 times (OR=2.71, CI–0.88:8.33). At the same time, patients with HPE often had complains on frequent and heavy menstruation, a general weakness in 1.31 (OR=1.31, CI–0.41: 4.18) and 1.01 (OR=1.01, CI–0, 10:9.40) times, respectively. While complaints on infertility and menstrual dysfunction have no significant relative risk values: OR=0.66, CI–0.20:2.25 and OR=0.8 CI–0.34:1.88, respectively.

Table III. Risk assessment for body systems in women with hyperplastic processes of endometrium compared with the control group.

No.	Gynecological anamnesis	Number of women	OR	Confidence interval	
			lower bound	upper bound	
1	diseases of cardiovascular system	22	2,04	0,57	7,34
2	diseases of the nervous system	35	2,71	0,88	8,33
3	pathology of the gastrointestinal tract	19	1,24	0,39	3,94
4	diseases of the urinary excretory system	6	0,48	0,11	2,03
5	diseases of respiratory system	10	1,28	0,27	6,20
6	endocrinopathy	24	1,01	0,37	2,75
7	varicose disease of the lower extremities	7	1,81	0,21	15,32
8	ophthalmic pathology	3	0,75	0,075	7,48
9	combined pathology	30	2,19	0,71	6,79
		Level of significance λ (alpha) = 0.05			

Table IV. Structure of detected pathology of endometrium by ultrasound, hysteroscopic examination and HS.

Diagnosis	Ultrasound	Hysteroscopy	Result of HS
Polyposis	62 5—false negative	69 2—false negative	67
Polyposis of endometrium with leiomyoma of the uterus	16 3—false negative	20	20
Polyposis of endometrium with adenomyosis	18 2—false positive	16 1—false positive	15
Polyposis of endometrium with leiomyoma of the uterus and adenomyosis	13 3—false positive	10	10

Taking into account these complaints, it is noteworthy that women with HPE have an increase in pain in 2.39 (OR=2.71, CI–0.88:8.33) times higher in comparison with healthy patients.

Analysis of the results of the gynecological anamnesis showed that the relative risk of HPE in patients with cervical erosion is 5.71, chronic inflammatory diseases of the uterine appendages—3.29, uterine myoma—6.21, ovarian cysts—2.95, polyps of the cervical canal—1,01, ectopic pregnancies—0.50, breast pathology—1.43 (Table 2). Thus, women with cervical erosion and uterine myoma have the risk of HPE respectively in 5.71 times (OR=5.71, CI–2.17:15.02) and 6.21 times (OR=6.21, CI–2.17:15.02) higher than in the control group. Interesting was the fact that the increase in the probability of the occurrence of HPE in women with past herpetic rash on the mucous membranes was by 5.05 times (OR=5.05, CI–1.66:15.36). Whereas the confidence interval in women, who had ectopic pregnancies in their anamnesis, does not have a significant difference (OR = 0.5, DI-0.04:5.66)

Thus, anamnestic data on cervical erosion, uterine myoma and episodes of herpetic rash on the mucous membranes can be assessed as specific and used to form risk groups.

Taking into account the results of our research, women with HPE have the risk of the pathology of the nervous system is in 2.71 times higher (OR=2.71, CI–0.88: 8.33), cardiovascular pathology—in 2.04 (OR=2.04, CI–0.57:7.34), vascular diseases of the lower extremities—in 1.81 times (OR=1.81, CI–0.21:15.32) compared with the control group. While the risk of pathology of the urinary system and organs of vision is only—OR=0.48, CI–0.11:2.03 and OR=0.75, CI–0.08:7.48, respectively.

Thus, the results of the evaluation of premorbid conditions in patients with HPE require timely diagnostic and medical–preventive activities regarding the occurrence of this pathology.

DISCUSSION

The results of the conducted analysis indicate a significant percentage of patients with combined endometrial pathology, which indicates the need to conduct a more detailed and in–depth study of the state of endo– and myometrium when uterine body polyps are detected using not only sufficiently informative, but also economically grounded diagnostic methods. These results are obviously crucial for the choice of treatment tactics. Frequent concomitant extragenital diseases necessitate an individual approach, both in the choice of adequate diagnostic methods and in effective treatment tactics.

Analyzing the results of the study using ultrasound examination, it was found that endometrial polyposis in combination with uterine leiomyoma was not detected in 3 women (15%), while all the results of hysteroscopy were confirmed by HS. When the endometrial hyperplastic processes were combined with adenomyosis—according to ultrasound examination a false positive result was obtained in 2 patients (13.3%), and in a hysteroscopic study we determined –1 false positive result.

In patients the diagnosis of "endometrial polyp" according to the results of hysteroscopy was not confirmed in 2 women (2 false positive results 2.99%) and in 5 cases of ultrasound examination (5 false negative results 7.46%). The clinical diagnosis in these patients was verified using HS.

The use of ultrasound examinations in patients with endometrial hyperplastic changes, according to our data, made it possible to identify pathology in 88.39% of cases, while the information content of the hysteroscopy was 98.21% ($p<0.001$). The results of the study confirm the opinion about the need to use the possibilities of ultrasound and hysteroscopic examinations as complementary methods for the diagnosis of endometrial hyperplastic processes. At the same time, the data obtained by us testify the advantages of visualization of endometrial polyps in a gynecological department of hospital in favor of a hysteroscopic examination.

Considering our findings, it can be said that visualization of polyps of the uterus with hysteroscopy is indeed a more informative diagnostic method and should be widely introduced into the clinical practice of treating women of reproductive age with endometrial hyperplastic processes in gynecological departments of hospitals.

CONCLUSIONS

Thus, the results of the subjective examination of patients in the gynecological department: complaints, anamnestic data on gynecological and extragenital pathology should be used to identify etiopathogenetic factors and the formation of risk groups for the occurrence of hyperplastic processes of endometrium.

Women with cervical erosion, uterine myoma and episodes of herpetic rash on the mucous membranes in past medical history have a higher likelihood of HPE.

The vast majority of patients (63.87%) with polyps of the body of the uterus have a combined hyperproliferative pathology, which requires an individual approach to planning the scope of diagnostic examination and the choice of treatment method.

Visualization of endometrium with hysteroscopy is more informative than ultrasound for diagnosing hyperproliferative processes, including uterine polyps.

Hysteroscopic polypectomy has a high level of both clinical and economic benefits as well as diagnostic value in patients with HPE.

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The work is carried out within the framework of the research work "Optimization of diagnosis and prevention of diseases of the reproductive system and development of pathogenically grounded methods for their correction" (state registration number 011U001801).

ORCID and contributionship:
Alla V. Boychuk: 0000-0002-2191-0383 [A, B, C, E, D]
Tetiana V. Vereshchahina: 0000-0003-4629-0771 [A, B, C]
Irina M. Nikitina: 0000- 0001-6595-2502 [F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna M. Nikitina
Sumy State University
1A/112 Lermontova st., 40030 Sumy, Ukraine
tel:+380662947360
e-mail: nikitina1med@gmail.com

Received: 11.04.2020
Accepted: 27.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

PECULIARITIES OF TRUNK SKIN AND FAT FLEXURES CHANGES OF RURAL AND CITY YOUTH IN THE CONDITIONS OF THE EDUCATIONAL PROCESS

DOI: 10.36740/WLek202009221

Nataliia S. Alekseyenko[1], Vitalii M. Andriychuk[1], Larysa Ya. Fedoniuk[2], Arina O. Ivanytsia[1], Olga V. Dzekan[1]
[1]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[2]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

ABSTRACT

The aim: Determination of the peculiarities of annual changes in the thickness of trunk skin and fat flexures of rural and urban youth during educational process.

Materials and methods: Were examined 200 healthy youths (100 residents of the village, 100 residents of the city) at their 1st, 2nd and 3rd courses of study at the University of Life Safety using Shephard R. method.

Results: Based on the data obtained, the annual reduction of all trunk fat index values of rural and urban youth during their studies at the University of Life Safety were established. Comparing intra-group annual changes, they were drastically smaller in the first year of study, both in the rural group and in the locals' group.

Conclusions: During the course of the study, we found a decrease in all the supervised indicators in both groups. However, intergroup changes during the first year of study were significantly ostent.

KEY WORDS: fat thickness, trunk, youngers, citizens, villages

Wiad Lek. 2020;73(9 p. II):2017-2022

INTRODUCTION

Globalization is considered to be the driving force behind change in world processes. The main feature of the 21st. globalization is that no country can develop and maintain its effective functioning beyond its borders through the interdependence of sectoral relations [1]. Medicine is not an exception. Particular attention is drawn to the medical industry in the context of the integration development of European countries. The effectiveness of the health care market is significant in the context of a long-term national strategy for socio-economic health policy [2, 3]. Modern socio-economic conditions of life place high demands on the ability to work, the level of physical development and functional state of the organism of the young generation [4]. Physical development is a sign of human health [5]. Human, during the life development, goes through a series of consecutive stages, each of which is characterized by its traits and structure of mental activity, the relationship of the individual with the environment [6, 7, 8]. At the time of driving up to higher education, youngers reach only a certain level of physical maturity, which still continues to develop [9].

Determination of total body size makes it possible to assess the level of morpho-functional development, as well as to characterize the processes of growth and physical development of man [10].

Thus, today there are scientific works in which the influence of endogenous and exogenous factors on anthropometric parameters of youth are considered [11, 12].

However, there are no works in which the annual changes of somatometric parameters, namely indicators of trunk fat thickness of rural and urban residents under the educational process, are determined and compared.

THE AIM

Determination of the peculiarities of annual changes in the thickness of trunk skin and fat flexures of rural and urban youth during educational process.

MATERIALS AND METHODS

Were measured 200 practically healthy young men, 100 of whom were urban dwellers, the other 100 youngers were rural areas habitants. At the time of the examination, they were all studying at the School of Civil Protection at Lviv State University of Life Safety, which is the departmental higher education institution (university) of the first level of accreditation of the State Emergency Service of Ukraine (SESN). All surveyed youths lived in a dormitory, had a standard daily schedule and meals in accordance with the Charter of the Armed Forces of Ukraine, pedagogical process and physical activity of all youths were standard and corresponded to the specifics of the SES profile institution.

Commission on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (report № 8 dated October

25, 2018) established that the studies did not deny the main bioethical norms of the Helsinki Declaration adopted by the General Assembly of the World Medical Association, Council of Europe Convention on Human Rights and Biomedicine, relevant provisions of World Health Organization, International Council of Scientific Medical Societies, International Code of Medical Ethics and the laws of Ukraine and may be used in scientific work. All young people signed a form of informed consent. Participants were provided with anonymity and confidentiality of data.

The thickness of the students` fat layer was determined during the first and second years of study, using the Shephard R. method [13]. The were divided into 2 groups depending on the place of residence. Between the groups of rural and urban residents we compared the obtained somatometric indicators and studied the dynamics of these indicators over three years of study. The statistical processing of the obtained results using parametric and non-parametric methods was carried out using the standard computer program "STATISTICA 6.1". We determined the normality of the distribution of the data for each of the variations obtained, the average values for each of the studied traits, standard errors and deviations. Student's t-test was used to assess the significance of differences in indicators of both groups, with a value $p<0.05$ the difference was considered significant.

RESULTS

The thickness of the fat layer under the scapula in the first year of study among the villagers was 4.68 ± 1.19 mm, the inhabitants of the city were smaller and equal to 4.53 ± 1.20 mm. During the second-year study, the population of this village decreased by 0.73 mm and equaled 3.95 ± 1.10 mm, while in the city residents decreased to 4.04 ± 1.19 mm. In the third year, the thickness of the fat layer under the scapula in the inhabitants of the village and the city again decreased: in the peasants - up to 3.94 ± 1.09 mm, in the locals - up to 4.03 ± 1.18 mm. The average change in the thickness of the fat layer under the shoulder blade for the village youth in the first year of study was (–0.73 ± 0.06) mm with a lowest amount value (–3.00) mm and a record gain of 0.50 mm. This annual change in young men from the city equaled (–0.49 ± 0.07) mm with minimum and maximum values – 2.50 mm and 1.50 mm, correspondingly. In the second year of study, the difference in thickness of the fat layer under the scapular for city dwellers was (–0.01 ± 0.01) mm, with a smallest amount and highest value of ± 0.50 mm. For the village dwellers the following indicators were: average - (–0.01 ± 0.01) mm, minimum - (–0.50) mm, maximum - 1.00 mm. The thickness of the fat layer under the scapula of the villagers during the training decreased by 0.74 mm, with the main decrease was supervised in the first year of study, and the intra-group annual change of this parameter in the first year of study was drastically smaller by 0.72 mm compared to the annual change in the second year ($t = 11.08$ at $p<0.05$).

In town-people - decreased by 0.50 mm and yet again the main reduce was observed in the first year of study. The annual change of this parameter in the first year of study is considerably slighter by 0.48 mm compared to the annual change in the second year ($t = 6.53$ at $p<0.05$).The inter-group annual change in the thickness of the fat layer under the scapula in the first year of study of the villagers was significantly smaller by 0.24 mm compared to the inhabitants of the city ($t = 2.55$ at $p<0.05$).In the period of second year of study, the inter-group annual change of this thickness among the inhabitants of the village and the city was the same and there was no considerable difference.

The thickness of the fat layer in the abdomen area in the first year of study was 4.15 ± 1.29 mm among the villagers, speaking about citizens, it was lower and equaled to 3.88 ± 1.21 mm. During the second-year study, the parameter had decreased by 0.51 mm with villages and equaled 3.64 ± 1.17 mm, while in the city residents it reduced to 3.56 ± 0.10 mm. In the third year, the thickness of the abdomen fat layer in the inhabitants of the village and the city dwellers decreased again: up to 3.63 ± 1.15 mm and up to 3.52 ± 1.05 mm responsibly.

The average change of the fat layer thickness in the abdomen area for the village youth during the first year of study was (–0.50 ± 0.07) mm with a bare minimum of (–4.00) mm and increase of 0.50 mm. This annual change in young men from the city was equal to (–0.31 ± 0.07) mm with minimum and maximum values (–3.50) mm and 2.00 mm, respectively. In the second year of study, the difference in the thickness of the fat layer in the abdomen for the villagers was (–0.01 ± 0.01) mm, with a minimum and maximum value of ± 1.00 mm.

The thickness of the abdomen area fat layer of the village residents decreased by 0.51 mm during the study, with the main diminish observed during the first year of study, and the intra-group annual change of this parameter in the first year of study was significantly minor by 0.49 mm comparing to the annual change in the second year ($t = 6.54$ at $p<0.05$). Town- people – showed the derision by 0.35 mm and the main drop off was observed in the first year of study. The annual change of the parameter during the 1st year of study was extensively greater by 0.27 mm compared to the annual change in the 2nd year ($t = 3.67$ at $p<0.05$).

The inter-group annual change of the abdomen fat layer thickness in the first year of villagers' education was smaller by 0.20 mm compared to the residents of the city, and in the second year - the inter-group annual change of the thickness in the villagers was greater by 0.03 mm compared to the city residents. It should be noted that this annual change in the first and the second year of study when comparing the groups of young people did not demonstrate a significant difference.

The thickness of the fat layer on the trunk side of the first-year villagers was 4.33 ± 1.30 mm, as for the city inhabitants, it was smaller and equaled 3.93 ± 1.35 mm. It should be noted that this thickness of the skin-fat layer in the villagers turned out to be drastically greater by 0.40 mm compared to the citizens ($t = 2.16$ at $p<0.05$).During the second-year study, the size of the village residents decreased by 0.58 mm and equaled 3.75 ± 0.80 mm, while the residents of the city – slowed down to 3.52 ± 0.90 mm .In the third year, the thickness of the fat layer on the villag-

ers 'trunk side increased and, in the citizens, - decreased: up to 3.77 ± 1.13 mm and 3.50 ± 1.12 mm respectively. The measurements on the 3rd year showed the increasing villagers thickness fat layer of the trunk side and derision of the parameter for city dwellers: - up to 3.77 ± 1.13 mm and to 3.50 ± 1.12 mm respectively.

The average change in the thickness of the fat layer on the side for village youth in the first year of study was (–0.58 ± 0.08) mm with a minimum value of (–3.50) mm and a maximum gain of 1.00 mm. This annual change in youths from the city was equal to (–0.40 ± 0.09) mm with minimum and maximum values of –3.00 mm and 3.00 mm, respectively.

In the second year of study, the difference in the thickness of the trunk side fat layer for the villagers was 0.03 ± 0.02 mm with a minimum and maximum value of ± 1.00 mm. The following indicators are characterized for city dwellers: average - (–0.02 ± 0.01) mm, minimum - (–1.00) mm, maximum - 1.00 mm.

The thickness of the fat layer on the side of the village residents during the training decreased by 0.55 mm, by the way, the lessen was observed only in the first year of study, and the intra-group annual change of this parameter in the first was appreciably smaller by 0.61 mm compared to the annual change in the second year ($t=7.27$ at $p<0.05$).As for the citizens, it decreased by 0.42 mm and the main drop off was observed in the first year of study. The annual change of this parameter in the first year of study was significantly smaller by 0.38 mm compared to the annual change in the second year ($t=3.93$ at $p<0.05$).

The inter-group annual change in the thickness of the fat layer on the trunk side during the first year of villagers' education was lesser by 0.18 mm compared to the residents of the city. As for the second year of study, the inter-group annual change of this thickness among the villagers was already greater by 0.05 mm compared to the locals. It should be noted that this annual change in the first and the second year of study, when comparing the groups of young people was a noteworthy different.

DISCUSSION

Anthropology is the science of a person that studies human biology, ethnography, physical organization and their changes in time and space, polymorphism of biological human organization at the individual and population levels under the influence of evolution, constitutional features and physical development [5]. Anthropometric parameters of youngers as well as changes of these indicators were studied by other scientists. Thus, when comparing the data obtained by us (indicators of the thickness of young city and village dwellers body fat layer) with the results of studies another sicentists we had found that no significant difference appeared between the results [14, 15, 16]. Due to the fact that the young people we examined, were in the same conditions of surrounding area influence and educational process, which was due to the uniformity of approaches to the organization and intensity of physical and mental load, belonging to rural or urban residence becomes a dominant factor. There are quite a number of studies aimed at examining the effects of habitat and residence conditions on physiological and psychological parameters. Such studies are usually conducted on groups of students or students of individual educational institutions [17]. In contrast to the above works, we obtained the results of the study of the parameters of the thickness of the fat layer of the trunk in the educational process and compared the changes of intragroup parameters during the period of studying. By the way, intergroup variations in these indicators and the characteristics of changes in rural and urban youth during training were identified.

CONCLUSIONS

The following differences were identified while comparing the changes in the thickness of the trunk fat layer under the influence of the educational process.

Parameters of the young men trunk thickness during the first year of study among the villagers turned out to be greater than that one of the city residents.

During the investigation, all the studied parameters decreased in both groups of youngers.

The intergroup indices of the annual change in the thickness of the trunk fat layer during the first year of education for the villagers were smaller compared to the inhabitants of the city, and the thickness of the fat layer under the scapula had drastically valuable changes.

The thickness of the fatty layer of the extremities, as well as the total and partial body sizes of rural and urban youths, are needed further, followed by a comparison of their annual changes during academic year.

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The work is carried out within the framework of the initiative research work of the E.Pirogov Vinnitsa National Medical University (Vinnitsa, Ukraine) "0114U000990 The influence of exogenous factors (socio-economic, ecological, geological, territorial) on anthropometric parameters and physiological indicators of adolescents".

ORCID and contributionship:
Nataliia S. Alekseyenko: 0000-0003-3137-7436 [B, D]
Vitalii M.Andriychuk: 0000-0001-8984-3028 [A, C]
Larysa Ya. Fedoniuk: 0000-0003-4910-6888 [F]
Arina O. Ivanytsia: 0000-0002-5296-7075 [E]
Olga V. Dzekan: 0000-0002-4115-9638 [E]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Larysa Ya. Fedoniuk
I. Horbachevsky Ternopil National Medical University
9 Valova st., 46000 Ternopil, Ukraine
tel: +380673999143
e-mail: Fedonyuk22Larisa@gmail.com

Received: 19.04.2020
Accepted: 28.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

SURGICAL TACTICS IN RECURRENT INGUINAL HERNIAS AT THE CHILDREN

DOI: 10.36740/WLek202009222

Volodymyr M. Baibakov
DNIPRO MEDICAL INSTITUTE OF TRADITIONAL AND NON-TRADITIONAL MEDICINE, DNIPRO, UKRAINE

ABSTRACT

The aim: Is to increase effectiveness of treatment at the children with recurrent inguinal hernias by improving surgical tactics.

Materials and methods: Method of laparoscopic correction of the recurrent inguinal hernias in children. For a period from 2017 to 2020 years in the surgical department of Municipal Establishment «Dnipro specialized clinical center of mother and child named by professor M. F. Rudnev» of Dnipro Regional Council» situated in the city Dnipro were carried out 48 laparoscopic procedures in a case of recurrent inguinal keel in children at the age of 3 years.

Results: We proposed an innovative method of laparoscopic correction the recurrent inguinal hernias, which allows to eliminate a hernial pocket without additional injury structures of the inguinal canal. At the analysis cases of recurrent inguinal hernias was concluded, that recrudescence appeared among young children and more frequently, after surgical interference on the strangulated inguinal hernias, which were operated by traditional ways.

Conclusions: According to the results of our research, it had been proved, that among numerous measures, focused on a restoration drainage system violation in the testicle, in a case of infringement obliteration of vaginal sprouts of a peritoneum in the boys and to keep safe ovarium vascularization in the girls.

KEYWORDS: inguinal hernia, recurrence, laparoscopy, children

Wiad Lek. 2020;73(9 p. II):2021-2025

INTRODUCTION

Relapses of inguinal hernias in children occuring at an early age, which is connected with difficulties of the anatomical and functional features in the structure of an inguinal region and immaturity of the connective tissues [1]. These factors determine technical difficulty of performing surgical intervention and demand from the surgeon a good knowledge of anatomy in the inguinal region at the children in the early age and high practical training [2, 3]. In the analysis of the national and foreign literature sources [4, 5] from the given subject draws attention a lack of common pathogenic view, which focused not only in the separate issues, but on the following fundamental issues as:

- determination of the optimal terms of re-operation;
- choice of the most minimally invasive and optimal methods of surgical correction;
- optimization principles of the postoperative management of patients [6, 7, 8].

When analyzing literature review and based on our own experience, we would come to the conclusion, that results of treatment recurrent inguinal hernias in children were not satisfy scientists and clinicians. It should be explained by a high percentage of postoperative complications, especially on the reproductive organs [9, 10, 11]. High traumatism of repeat surgical intervention in a groin area with scarring and disruption normal anatomic relationship between structures in a groin area should lead to the negative consequences on the reproductive organs at the boys and girls in a fertile age.

Therefore, using of laparoscopic correction of the recurrent inguinal hernia after traditional intervention in a groin area significantly reduces risk of additional trauma in the structures of an inguinal region in children. Solution of this problem is an important step in a direction of safety reproductive health of the nation and preservation of complete family [12, 13, 14].

THE AIM

Aim of research is to increase effectiveness of treatment at the children with recurrent inguinal hernias by improving surgical tactics.

MATERIALS AND METHODS

Method of laparoscopic correction of the recurrent inguinal hernias in children. For a period from 2017 to 2020 years in the surgical department of Municipal Establishment «Dnipro specialized clinical center of mother and child named by professor M. F. Rudnev» of Dnipro Regional Council» situated in the city Dnipro were carried out 48 laparoscopic procedures in a case of recurrent inguinal keel at the children, which were undergoing the first intervention by traditional access in a groin area. All children were at the age of 3 years. Analysis cases of recurrent inguinal hernias had been shown that recrudescences appeared at the young children and more frequently, after surgical interference on the strangulated inguinal hernias, which were operated by traditional ways (95%).

RESULTS

The method is performed as follows. Under the endotracheal narcosis by transumbilical way we submit port D-5 mm, through which we conduct laparoscope D-5 mm into the abdominal cavity. Pressure of CO_2 in the abdominal cavity is supported on the level 8-10 mm of mercury column. Examine the internal inguinal rings, we should established a presence of recurrent inguinal hernia. During applying of carboxiperitoneum, intraoperatively, we performed the ultrasound-control of a groin area from the side of surgical intervention. Evaluate presence of gas in a hernial pocket, its shape, size and location, condition of the aponeurosis. In a case where the hernial pocket is filled with gas in the stretch, and condition of aponeurosis corresponded to the plastic, we performed only suturing of an internal inguinal ring after hydraulic dissection and injection of tissue adhesive into the lumen of a hernia pocket. Performed hydraulic preparation of tissue around the internal inguinal ring with 0.9% sodium chloride solution. After that we proceed to the imposition of a purse-string suture in a place of internal inguinal ring. For this purpose we should used prolene 2-0. We take in a seam peritoneum in the place, where were held hydraulic preparation of the tissues. Under a video control, in the point of projection an internal inguinal ring, this is determined by pressing on the anterior abdominal wall, we input to a groin channel the dulled end needle G-19 with prolene 2-0 thread, which is not absorbed. Hereafter we should apply hydraulic preparation with 0.9% sodium chloride solution carried out by the following way. Thread should pass under the peritoneum on one of the walls in the inguinal canal. Having enter a thread, we should form the loop. Then the needle is removed, and a loop is left in the abdominal cavity. The needle is inserted in the other end of the thread and through the same puncture thread is entered under the peritoneum opposite a wall of inguinal canal. The end of a thread should be passed through already formed loop.

Then remove a needle, both ends of a thread output on the anterior abdominal wall. Before tightening of a formed around the internal inguinal ring suture, to a lumen of the inguinal canal we injected one-component adhesive tissue with active substance of n-butylcyanoacrylate, after the node could be tighten.

The ends of a thread should be cut, estimate control of the purse-string suture tightness. Defect of aponeurosis eliminated by mini access in a groin area. For diagnosis of necrotic changes or if it is suspected, we recommend to continue operation by an open access. If, according to the ultrasound, there is divergence of aponeurosis with the next formation of defect, it should be carry out a mini skin incision to 2.0 cm in length and having sutured defect of aponeurosis without removal of a hernia pocket. Suturing of the internal inguinal ring was done after hydraulic dissection and injection of a tissue adhesive into the lumen of hernia pocket from the side of abdominal cavity.

Hydraulic preparation of tissues in a region of internal inguinal ring from the side of abdominal cavity with applying 0.9% NaCl solution should be used only as the additional method of prevention bleeding, as the result of vessels injury. Hydraulic preparation of the internal inguinal ring tissues, with using 0.9% NaCl solution, significantly reduces risk of the spermatic cord vessels injury in the in boys, and should prevent oncogenes of hydrocele or testicular atrophy.

N-butylcyanoacrylate (enbucrilate) is medical glue in a liquid form, which facilitates drawing it through the lumen of hernia pocket with applying the biocompatible, haemostatic, antibacterial, non-histotoxic drug. It should prevent formation of secondary inflammatory responses, and blue color induces in the field of operational space. Its introduction into the lumen of hernia pocket increased reliability of the purse-string suture; eliminates risk of recurrence hernia, hydrocele or testicular atrophy in the boys, decreases time of surgical treatment. Properties of glue are sufficient to overcome efficiency, reduce morbidity and providing of a satisfactory cosmetic effect.

The average duration in a hospital was 2 days. High efficiency of the given method was confirmed clinically and with ultrasound control.

DISCUSSION

Results of research provide an opportunity to minimize in practice development of complications and decreased risk of postoperative complications. Thus, proposed method of laparoscopic correction of recurrent inguinal hernias allows to eliminate a hernial pocket without the additional injury structures of the inguinal canal, which are being in a condition of cicatricial process, forming after the previous surgery in the inguinal region. Besides, a good cosmetic effect of operation prevents re-formation of the adhesions and rough scars. Finally, advanced diagnostics and choice optimal method of surgical treatment the recurrent inguinal hernias in children should be actual issues. Scientific developments of recent years should be focused on feasibility of the anatomically and pathogenetically reasonable surgical interventions.

Review methods for the diagnosis of recurrent inguinal hernias in children was carried out. The diagnosis of recurrent inguinal hernias received a lot of attention in the world and national literature. There were used a variety of research methods. Pelviography has been proposed for the detection of recurrent inguinal hernias in children. With the development of science, new methods of examining patients appeared. Immediately after its appearance, ultrasonography occupied a firm place among the methods of recurrent inguinal hernias in children diagnostics, since it allowed determining the location, size and structure of the gonads with a sufficiently high accuracy. The use of the technique based on the doppler effect, which allows to investigate a blood flow in the testicular parenchyma. At the same time, the assessment is not only qualitative, but also quantitative, since it became possible to measure the blood flow parameters: blood flow velocity during systole, blood flow velocity during diastole, resistance index.

If ultrasound diagnostics of internal organs devoted many works described in the world literature, then the works that are devoted to the dopplerography of the gonads, especially in children, are rare. Meanwhile, this diagnostic method allows evaluating hemodynamic in the gonad at a qualitative and quantitative level, and indirectly judging the state of the testicular parenchyma. Diagnostic laparoscopy has become a method that has become an integral and indispensable part of the diagnosis of recurrent inguinal hernias in children and

determination of treatment tactics. Minimally invasiveness in combination with highly informative made this method the leading one in diagnosing these forms of pathology.

Relapses of inguinal hernias we recommended to operate by laparoscopic way of surgery with an intraoperative ultrasound control. The main reasons of recurrence inguinal hernias in children we consider infringement of technique during the first operation. It should be the following disadvantages:
- removal only a distal part of the hernia;
- removal not a hernia pocket, but the surrounding tissues;
- violation methods of suturing aponeurosis of the external oblique muscle in the abdomen;
- performing of surgical operations should be providing by pediatric surgeons, but not by the surgeons of general practice without sufficient experience.

Given factors give an opportunity for the pediatric surgeons to search new, less traumatic and highly effective methods of surgical treatment the recurrent inguinal hernias in children. These objectives correlated with proposed by us innovative method of laparoscopic correction the recurrent inguinal hernia with carrying out an intraoperative ultrasonography for an inguinal control of a groin area from the side of intervention.

CONCLUSIONS

1. In the recurrence of inguinal hernia numerous disorders of testicular blood flow at the boys and impaired ovarium vascularization at the girls are risk factors of infertility in the reproductive period.
2. Among measures, which focused on the restoration violations of testicle drainage system in a case of infringement obliteration of vaginal sprouts of a peritoneum in the boys and preserve ovarium vascularization in the girls during re-intervention a basic role takes implementation of the pathogenetically substantiated method of surgical correction pathology on the level of a deep inguinal ring with using modern laparoscopic techniques.
3. Ultrasound method of research with using of doppler technology is a highly efficient way of assessing the anatomical indicators as well as estimation size of testicles in boys and ovaries in girls, vessels, parenchyma of the reproductive organs, and functional indicators.

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Research work was carried out within a framework the cathedral theme of the research work: "Morphological state of vascular-tissue relations in the structure of organs and tissues and development of organ-preserving operations using laser technique", state registration number 0104U010388 (implementation period 2017-2021 years).

ORCID and contributionship:
Volodymyr M. Baibakov: 0000-0001-8632-103X [A, B, C, D, E, F]

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Volodymyr M. Baibakov
Dnipro Medical Institute of Traditional
and Non-Traditional Medicine
13 Zadunaiska St,. village Sursko-Lytovske,
52064 Dnipro, Ukraine
tel: +380509198547
e-mail: baybakov837@gmail.com

Received: 03.10.2019
Accepted: 29.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

THE VALUE OF DENTAL EXAMINATION FOR EARLY DIAGNOSIS OF THE MUSCULOSKELETAL SYSTEM DISEASES

DOI: 10.36740/WLek202009223

Marina A. Shundryk, Iryna Y. Marchenko, Iryna M. Tkachenko, Viktor V. Boiko, Valeriy Y. Marchenko, Olga V. Sheshukova
UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

The aim: The purpose of the study was to determine the correspondence between the location of the tongue median line and the degree of distortion of the vertebral column at different levels in children with scoliosis.

Materials and methods: Totally 56 children (30 girls, 26 boys) aged 11-14 years were examined, with a duration of musculoskeletal disorders 1-3 years. For each participant an oral cavity examination was performed, the position of the middle line of the tongue was determined. X-ray images of vertebral column of the patients from investigated groups were analyzed.

Results: In the group with 1year duration of the disease 25.02% patients had a violation of the medial line of the tongue, in the group with 2 years of duration of the disease - 65,52% participants had the deviation of the medial line of the tongue, in the group with 3 years of duration of the disease 86.66% of patients had the deviation of the medial line of the tongue.

Conclusions: This research allows us to recommend paying attention not only to the size, color, state of the papillae of the tongue, but also to the position of the middle line, which distortion may significate the deviation of the vertebral column in different portions.

KEY WORDS: posture, scoliosis, central line of the tongue deviation

Wiad Lek. 2020;73(9 p. II):2024-2026

INTRODUCTION

Until recent years pathologies of organs of the oral cavity and the mucouse membrane were considered as local pathological processes associated only with the bad hygienic condition of the oral cavity and the negative influence of pathogenic factors. However, modern researches and experimental models of the diseases allow us to establish that the oral cavity has a close anatomical and physiological relationship with various systems of the organism [1, 2, 3].

Even ancient physicians used a tongue to decipher diagnostic symptoms of almost any human disease from its surface. Indeed, it can be stated that the violation of various organs usually manifested with changes in the surface of the tongue even before their pathological symptoms appear. Even with the disappearance of symptoms the tongue may indicate that the etiology of the disease remains unresolved and the full recovery did not happen.

Increasing sensitivity and discoloration of certain parts of the tongue reflects the disturbance of those organs associated with corresponding areas on its surface.

The localization of the plaque which covers the tongue indicates the accumulation of toxins in the stomach and small intestine (if the plaque is localized in the middle part of the tongue), in the large intestine (if the plaque is localized in the distal third of the tongue).

The surface of the tongue may reflect disorders in digestion, cardiac activity, nervous and endocrine systems.

In the literature there is data that the tongue can help in the diagnosis of many diseases, because its general appearance is in big relation with its anatomical features. Receptors of its mucous membrane are closely related with the central nervous, cardiovascular, endocrine and locomotor systems. [3, 5].

THE AIM

The purpose of the study was to determine the correspondence between the location of the tongue median line and the degree of distortion of the vertebral column at different levels in children with scoliosis.

MATERIALS AND METHODS

In order to achieve this goal, we performed our research on the basis of the Poltava regional sanatorium for children with musculoskeletal disorders. Totally 106 children (68 girls, 38 boys) aged 11-14 years were examined, with duration of musculoskeletal disorders 1-3 years (Tab 1). The comparison of the location of the median line of the tongue (photos) with the position of the spine (X-ray) in different departments - cervical, thoracic, and lumbar was also performed.

RESULTS AND DISCUSSION

Scientific researches suggest posture problems as a factor affecting the occurrence of occlusion anomalies as well

Table I. Dispersion of patients regarding to their age and duration of the disease.

Age	N of patients		Duration of the disease (years)		
	n = 106	%	1	2	3
11	21	19.1	8	13	0
12	23	20.9	7	13	3
13	15	17.3	3	7	5
14	47	42.7	11	19	17

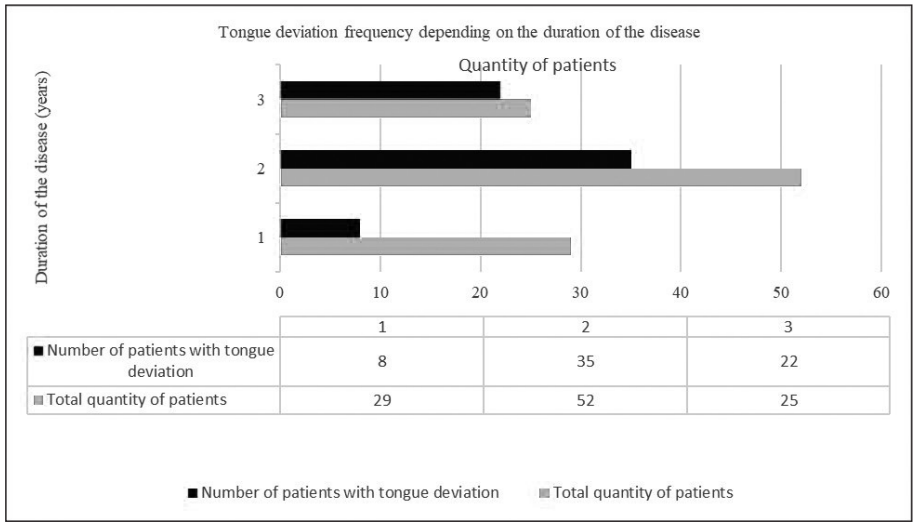

Fig. 1. Dispersion of the patients with the central line of the tongue deviation

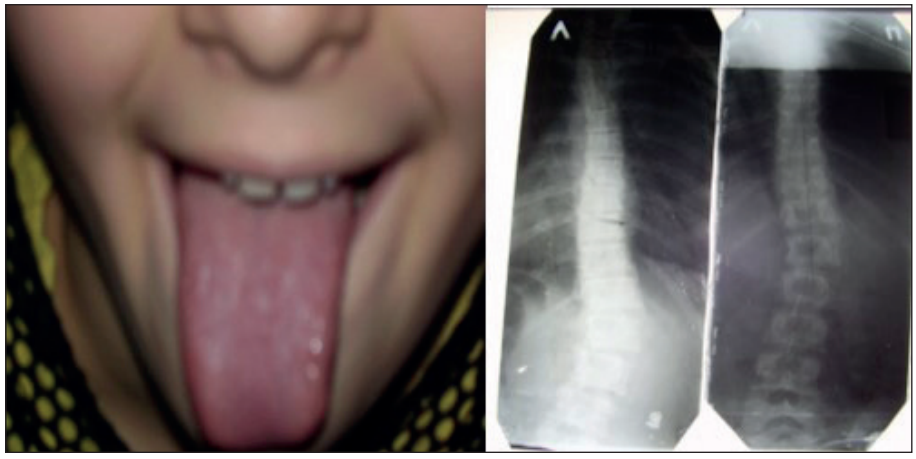

Fig. 2. Patient K., 11 years. Distortion of the middle line of the tongue in its upper third area corresponds to the distortion of the spine in the lumbar region.

as their complications. In the case pathological occlusion (usually distal occlusion) an increased load on the constantly tensed occipital, ladder, thoracic-clavicular-osseous muscles) due to displacement of the center of gravity of the head augmentation. [4, 5]. Taking into consideration the high mobility of the cervical portion of the vertebral column some preconditions for disfunction of all systems and organs appear. Especially for those located in the maxillo-facial area and exercising on the facial skull, cranial and spinal nerves, autonomic ganglia, vascular bundles, different muscles of the mentioned area, including mylohyoid and hyoglossus muscles, which cooperate with proper longitudinal and vertical muscles of the tongue.

The line which goes in the middle of it, accurately reflects the state of the human backbone. The curvature of the line on the tip of the tongue signs about the curvature of the vertebral column in the cervical portion, the one in the middle signs about problems in the thoracic part, at the root deviation corresponds to the curvature of the vertebrae in the lumbar section.

For the human spine three moderately pronounced physiological bends are natural. Cervical spine has a curve, convex forward, that begins at the axis at the apex of the odontoid process and ends at the middle of the second thoracic vertebra (lordosis). The thoracic curve, concave forward, begins at the middle of the second and ends at

the middle of the twelfth thoracic vertebra (kyphosis). The lumbar curve begins at the middle of the last thoracic vertebra and ends at the sacrovertebral angle (lordosis).

Scoliosis is a pathological lateral curvature of the vertebral column with the obligatory rotation of the vertebral bodies. The characteristic feature of which is a progression of the disease, associated with age and growth of the child.

Unfortunately, nowadays disorders of the backbone are very common among children and adolescents. Especially scoliosis, which is 5-6 times more likely to occur in girls than in boys and also affects the reproductive function which makes it is a socially significant disease [6, 7].

Whereas the spine deformation reflects can affect the median fissure of the tongue appearance, dentists as first-line doctors communicating with wide sections of the population during examinations in kindergartens, schools or in clinics can easily suspect the pathology and inform the patient or his/her parents about it, thereby to prevent further development of the disease.

According to the dated received during the research it can be stated that the largest number of patients were children with duration of the disease for 2 years – 52 patients (47.3%), for 1 year - 29 patients (26.4%), 3 years - 25 patients (22.7 %).

In the group with 1year duration of the disease 27,6% patients had a violation of the medial line of the tongue, In the group with 2 years of duration of the disease 67,3% participants had the deviation of the medial line of the tongue, In the group with 3 years of duration of the disease 88,0% of patients had the deviation of the medial line of the tongue (Fig. 1).

The curvature of the spine in the cervical region corresponded to the bend of the medial line of the tongue in the tip region, the bend of the spine in the thoracic region corresponded to the bend of the medial line of the tongue in the middle part, the bend of the spine in the lumbar region corresponded to the bend of the medial line of the tongue in the root area (Fig.2).

Statistical tests were significant and confirmed the dependence between the increase of tongue deviation frequency and the duration of spine disease. T-test: p=0.00; t=21.28; df=107. ANOVA one-way test (deviation by duration comparison): p=0,00; F=14,29; df=2 between groups, within each group df=105.

CONCLUSIONS

Observation data give us the right to conclude that dentists can suspect the presence of spinal deformation without general examination and X-ray examination in patients with a disease duration period of at least 2-3 years during the preventive examination of children and adolescents.

This research allows us to recommend paying attention not only to the size, color, state of the papillae of the tongue, but also to the position of the middle line, which distortion may significate the deviation of the vertebral column in different portions.

This study suggests further elucidation of the mechanism of influence of the vertebral column condition and skeletal muscles influence on the muscles of the maxillofacial area, which are involved in the formation of occlusion and function of oral cavity organs.

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ORCID and contributionship:

Marina A. Shundryk: 0000-0003-3186-5923 [A,B]
Iryna Y. Marchenko: 0000-0001- 7092-1786 [C]
Iryna M. Tkachenko: 0000-0001-8243-8644 [D]
Viktor V. Boiko: 0000-0002-1568-7576 [E]
Valeriy Y. Marchenko: 0000-0002-3048-7249 [F]
Olga V. Sheshukova: 0000-0002-4739-4890 [F]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Marina M. Shundrik
Ukrainian Medical Stomatological Academy
17 Zalizna St., 36001 Poltava, Ukraine
tel: +380508633626
e-mail: shundrikliliya@gmail.com

Received: 24.03.2020
Accepted: 29.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

PLACEMENT OF A PERSON IN A MEDICAL INSTITUTION IN ORDER TO CONDUCT A PSYCHIATRIC EXAMINATION: INTERNATIONAL STANDARDS AND NATIONAL REALITIES

DOI: 10.36740/WLek202009224

Olga I. Tyshchenko[1], Ivan A. Titko[2]
[1]YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE
[2]POLTAVA LAW INSTITUTE OF YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

The aim: The aim of this work is to identify the compliance level of modern practice of placement of a person in a medical institution in order to conduct the FPE to international standards and legal positions of the ECHR in terms of ensuring the right to liberty and security of person; formulation of scientifically substantiated proposals on the synchronization directions of national practices with the specified international standards.

Materials and methods: During the preparation of the article the following was processed: scientific research on ensuring the rights of persons suffering from mental disorders in criminal proceedings; provisions of international agreements on the provision of psychiatric care; legal positions of the ECHR on the observance of persons' rights suffering from mental disorders (15 judgments on this topic); criminal procedural legislation of individual states; results of generalization of national law enforcement practice; the results of a survey conducted by the authors of 18 psychiatrists who practice in the field of forensic psychiatric examinations (psychiatrists working in state psychiatric clinics in Odesa, Poltava, Kharkiv were interviewed).

In the process of research a set of general scientific and special methods of cognition was used (comparative-legal method, system-structural method, generalization method, method of analysis and synthesis, method of sociological research, method of expert assessments, etc.).

Results: According to the research results: a) legal positions of the ECHR on the observance of the rights of persons suffering from mental disorders are identified and generalized; b) the compliance level of modern practice of placing a person in a medical institution in order to conduct the FPE with international standards and legal positions of the ECHR in terms of ensuring the right to liberty and security of person (§ 1 of Article 5 of the Convention); c) the degree of extrapolation of these positions to the activities of psychiatrists is analyzed; d) the optimal ways of solving the existing problems in the aspect of ensuring the rights of a person when placing them in a medical institution for an inpatient FPE are proposed.

Conclusions: The current national practice of placing a person in a medical institution for an inpatient FPE does not fully comply with the legal positions of the ECHR in terms of ensuring the right to liberty and security of person (in particular, there are deviations from the positions of the ECHR on: determining the documentary basis for the appointment of an inpatient FPE; interaction of police and medical workers in the field of psychiatry during the detention of a person with a mental disorder).

KEY WORDS: outpatient psychiatric examination, diagnosis of mental disorders, expert opinion, medical certificate, right to liberty, ECHR practice, forensic psychiatric examination

Wiad Lek. 2020;73(9 p. II):2030-2037

INTRODUCTION

According to the World Health Organization, mental disorders are one of the top public health challenges in the WHO European Region, affecting about 25% of the population every year [1]. At the same time, painful mental states are often the cause of deviant behavior, which is often expressed in the commission of socially dangerous acts by a person. In view of the above, the legislation of most states provides for the possibility of applying special medical response measures to such persons. However, the use of the latter is usually possible only after appropriate diagnostic measures. In turn, the possibilities of outpatient diagnosis of mental disorders are sometimes limited, and therefore there is a need for an inpatient FPE. In addition, this expertise, due to its specificity (significant restriction of personal liberty) may in some cases border on human rights violations (in particular, the prohibition of torture (Art. 3 of the Convention), the right to liberty and security of person (Art. 5 of the Convention)). Therefore, the conformity of national approaches to this issue to the formulated international standards (primarily in the ECHR judgments) is of particular importance.

THE AIM

The aim of this work is to identify the compliance level of modern practice of placement of a person in a medical institution in order to conduct the FPE to international standards and legal positions of the ECHR in terms of ensuring the right to liberty and security of person; formulation of scientifically substantiated proposals on the synchronization directions of national practices with the specified international standards.

MATERIALS AND METHODS

During the preparation of the article the following was processed: scientific research on ensuring the rights of persons suffering from mental disorders in criminal proceedings; provisions of international agreements on the provision of psychiatric care; legal positions of the ECHR on the observance of persons' rights suffering from mental disorders (15 judgments on this topic); criminal procedural legislation of individual states (Belarus, Lithuania, Moldova, the Russian Federation, Estonia, Uzbekistan, Ukraine, Poland); results of generalization of national law enforcement practice (more than 30 judgments of courts of Ukraine for 2019–2020 were processed); the results of a survey conducted by the authors of 18 psychiatrists who practice in the field of forensic psychiatric examinations (psychiatrists working in state psychiatric clinics in Odesa, Poltava, Kharkiv were interviewed).

In the process of research a set of general scientific and special methods of cognition was used (comparative-legal method, system-structural method, generalization method, method of analysis and synthesis, method of sociological research, method of expert assessments, etc.).

RESULTS

Placement of a person in a medical institution in order to conduct the FPE in the context of international standards and legal positions of the ECHR on ensuring the right to liberty and security of person (§ 1 (e) of Art. 5 of the Convention). International standardization of psychiatric care in general, and placement of a person in a medical institution for the conduct of the FPE in particular, is provided by international treaties and acts of a recommendatory nature, among which it is worth mentioning the Universal Declaration of Human Rights, 10 December 1948; European Convention on Human Rights, 04 November 1950; Declaration on the Rights of Mentally Retarded Persons, adopted by the UN General Assembly, 20 December 1971; Declaration on the Rights of Disabled Persons, adopted by the UN General Assembly, 9 December 1975; Recommendation (818) on the situation of the mentally ill, Council of Europe Parliamentary Assembly, 8 October 1977; Recommendation No. R (83) 2 of the Committee of Ministers to member states concerning the legal protection of persons suffering from mental disorder placed as involuntary patients, Council of Europe, 22 February 1983; The Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care, Resolution adopted by the UN General Assembly, 17 December 1991; Psychiatry and human rights, Council of Europe Parliamentary Assembly Recommendation 1235, 12 April 1994; Mental Health Declaration for Europe: Facing the Challenges, Building Solutions, adopted at the WHO European Ministerial Conference on Mental Health in Helsinki, Finland, 14 January 2005 etc.

Undoubtedly, the coercive conduct of the FPE is regulated at the level of domestic legislation of individual states (in particular, in the criminal procedural context it is worth mentioning Art. 509 of the Criminal Procedure Code (CPC) of Ukraine, Art. 443 of the CPC of Belarus, Art. 569 of the CPC of Uzbekistan, Art. 435 of the CPC of the Russian Federation; Art. 74 of the CPC of Poland, etc.). Since the legal nature of this institution is common to these states, a comparative analysis of its regulations is of scientific interest in terms of possible regulatory borrowing, which will be discussed further.

Placement of a person in a medical institution for conducting the FPE is in fact a compulsory isolation measure, which restricts a person's right to freedom around the clock during the term of appointment of the FPE. However, in accordance with § 1 (e) of Art. 5 of the Convention, everyone has the right to liberty and security of person. No one shall be deprived of his liberty save in the following cases and in accordance with a procedure prescribed by law: the lawful detention of persons for the prevention of the spreading of infectious diseases, of *persons of unsound mind*, alcoholics or drug addicts or vagrants. In the context of the interpretation of Art. 5 of the Convention, researchers consider the meaning of the words "arrest" or "detention" as a loss of liberty [2, p. 292-303]. In particular, as follows from the content of § 1 (e) of Art. 5 of the Convention, it is a question of *lawful detention of persons of unsound mind*. Namely, it is about detention of a person who has actually been diagnosed with a certain type of mental disorder. In this context, it is of particular importance to clarify whether the placement of a person in a medical institution in order to conduct the FPE qualifies as imprisonment in accordance with § 1 of Art. 5 of the Convention. Thus, in the case law, the ECHR has repeatedly noted that § 1 of Art. 5 of the Convention requires that in any case of liberty deprivation to ensure the purpose of Art. 5 of the Convention, namely the protection of individuals against arbitrariness (See at: § 35 of the Case of *Kornev* and *Karpenko v. Ukraine*; § 46 of the Case of Aerts v. Belgium [3, 4]). In this case, the Court emphasizes that deprivation of liberty is not limited to the classic cases of deprivation as a result of arrest or sentencing, but may take numerous other forms (§ 95 of the Case of Guzzardi v. Italy). Thus, in order to determine whether deprivation of liberty has taken place, the starting point can be a specific situation in which a number of factors should be taken into account, such as: type, duration, consequences and method of application of this measure (See at: § 92 of the Case of Guzzardi v. Italy; § 67 of the Case of Nielsen v. Denmark; § 42 of the Case of H.M. v. Switzerland) [5, 6, 7]). Thus, in the case law of the ECHR it is emphasized that the concept of deprivation of liberty combines both an objective element (keeping a person in a confined space for a significant period of time) and a subjective element (lack of reliable consent of a person to such detention) (See at: § 74 of the Case of *Storck* v. Germany; § 117 of the Case of Stanev v. Bulgaria; § 67 of the Case of Akopyan v. Ukraine) [8, 9, 10]. Interpreting the above legal positions of the ECHR in the context of placement of a person in a medical institution in order to conduct the FPE, we should note that in terms of deprivation of liberty concept, this measure combines an objective element (inpatient detention of a person in a medical institution for

a period of two months) and a subjective element (lack of reliable consent of the person to such inpatient detention in order to conduct the FPE). That is, by its legal nature, this measure is related to the restriction of a person's right to liberty (Article 5 § 1 (e) of the Convention), as in fact they are forced to remain territorially within the relevant medical institution for a long time (See also § 105 of the Case of Anatoliy Rudenko v. Ukraine [11]). However, in the absence of a subjective element (i.e., the person voluntarily agrees to be placed in the inpatient medical facility for the FPE), is it legitimate to consider this measure within the concept meaning of "deprivation of liberty"? In particular, the answer to this question is contained in the legal position expressed by the ECHR in § 64-65 of the Case of De Wilde, Ooms and Versyp ("Vagrancy") v. Belgium (Merits), in which the applicants voluntarily appeared before the police to be taken into custody. However, the Court has ruled that the right to liberty and security of person is too important in a democratic society for a person to be deprived of the guarantees of protection enshrined in the Convention solely on the basis of voluntary attendance at the police station [12]. The Court expressed a similar legal position in § 119 of the Case of Stanev v. Bulgaria [13]. Accordingly, the above legal position of the ECHR can be legally applied in the case of voluntary consent of a person to placement in a medical institution for the purpose of conducting the FPE. In this case, it is also a question of deprivation of the right to liberty and security of person, the guarantees of protection of which (provided for in Art. 5 of the Convention) do not lose their effect.

The conclusion of the outpatient examination on the mental state of the person as a documentary basis for placing a person in a medical institution in order to conduct the FPE. In its case law, the ECHR has repeatedly pointed out that the deprivation of liberty of a person of unsound mind cannot be regarded as meeting the requirements of Art. 5 § 1 (e), if the decision on such deprivation was made without the opinion of a medical expert (See at: § 59 of the Case of Ruiz Rivera v. Switzerland; § 31 of the Case of S.R. v. the Netherlands [14, 15]). However, the application of these legal positions during the appointment of an inpatient FPE can not be considered relevant, because the decisions of the ECHR refers to the established fact that a person has a mental disorder, and at the time of appointment of an inpatient FPE, the person's diagnosis is unknown (in fact, such an examination is appointed in order to obtain it). However, in the decision of the Case of Varbanov v. Bulgaria, the ECHR emphasized that no deprivation of liberty of a person considered to be of unsound mind may be deemed in conformity with Article 5 § 1 (e) of the Convention if it has been ordered without seeking the opinion of a medical expert. This rule applies even if the *purpose of the applicant's detention is to obtain a medical opinion* (§ 48 of the Case of Varbanov v. Bulgaria) [16]. A similar conclusion was reached by the ECHR in the Case of Kepenerov v. Bulgaria, in which the applicant failed to comply with the prosecutor's order to undergo a psychiatric examination, was detained on that basis and forcibly taken to a medical facility, where he was detained for 30 days. The court ruled that the domestic law governing the isolation of persons on mental health grounds did not authorize the prosecutor to subject the applicant to involuntary solitary confinement in a psychiatric clinic for the psychiatric examination. In addition, the current Bulgarian legislation did not oblige the authorities to obtain a medical opinion for isolation. The court noted that the applicant's detention had been unlawful within the meaning of Art. 5 § 1 of the Convention, as… did not require the seeking of an expert medical opinion to be placed in a specialized institution (§ 35 of the Case of Kepenerov v. Bulgaria) [17].

That is, a literal interpretation of the above legal positions of the ECHR allows to state that the purpose of inpatient detention in an expert institution is to obtain an expert opinion on the mental state of the person. In turn, the documentary basis for sending a person to the medical institution for an inpatient FPE is the initial conclusion of the outpatient examination, in which, if it is impossible to answer questions during the outpatient FPE, the expert must justify the need for the FPE inpatient form.

Survey results: 55.6% of psychiatric experts we surveyed expressed the belief that an inpatient FPE can be conducted only on the basis of a preliminary outpatient examination of the person's mental state, in which the expert must justify the need to conduct it in a stationary form (in case of impossibility to provide a categorical conclusion on the diagnosis of the person).

Medical certificate of mental disorder of the person as an alternative to a preliminary expert opinion. In this context, it is worth noting the differences in national practices. For example, the CPC of Ukraine does not clearly provide for the existence of such a certificate as a basis for sending a person to an inpatient FPE. While Part 1 of Art. 569 of the CPC of Uzbekistan determines the grounds for the appointment of an inpatient FPE as the conclusions of the outpatient examination and other medical documents. At the same time, Ukrainian jurisprudence shows that on the basis of this medical document, judges quite often satisfy the request of the investigator, the prosecutor to send a person to an inpatient FPE. However, based on the above legal positions of the ECHR, a medical certificate of a person with a mental disorder can not be a basis for the appointment of an inpatient FPE. In this case, there is a false identification of the conclusion of the outpatient psychiatric examination and a medical certificate confirming the presence of a person's mental disorder.

Survey results: 66.7% of the psychiatric experts we surveyed indicated that a medical certificate stating that a person has a mental disorder (instead of an outpatient examination report) could not be a basis for placing a person in a medical institution for the FPE.

Term of an inpatient FPE and its extension. The urgency of this issue is obvious primarily to states whose legislation sets a time limit on the duration of the FPE, but does not provide for the possibility of increasing such duration if necessary. An example of this is Ukraine, where the law provides that in case of need for long-term observation

and examination of a person may, an inpatient psychiatric examination may be performed, for which such a person is sent to the relevant medical institution for a period *not exceeding two months* (Part 2 of Art. 509 of the CPC of Ukraine). However, the question of the maximum duration of a person's stay in a medical institution during an inpatient FPE and the procedure for its extension remains unresolved (in contrast, for example, to such states as Estonia, Lithuania, Moldova, Uzbekistan). The problem is that with this approach, if the two-month period was exhausted during the initial examination, the possibility of conducting a repeat or additional inpatient FPE is questionable. However, in the presence of a probable conclusion of the primary FPE on the person's mental state, the exhaustion of the two-month period, combined with the absence of a procedural mechanism for its extension, would lead to a vicious circle of legal impasse. Namely, it would be procedurally incapable to legally resolve the issue of sentencing in relation to a person whose mental state is unknown.

Survey results: To the question "Were there any situations in your practice in which it was impossible to determine the mental state of a person by conducting an inpatient FPE?" only one of the 18 psychiatrists surveyed answered in the affirmative. This testifies to the rarity of such situations, but at the same time indicates their existence.

As it is rightly emphasized by Tijs Kooijmans, Gerben Meynen, "If behavioral experts cannot reach the conclusion – based on their own research and/or based on previous behavioral examinations of the defendant – that the defendant suffers from a mental disease or mental defect, the judge should refrain from an assessment that the defendant nevertheless suffers from a psychiatric illness. The consequence of this line of reasoning is that the judge would indeed be limited with regard to the possibilities of disposal of the criminal case" [18, p. 6].

Therefore, the need to regulate the procedure for extending the term of an inpatient FPE is more than obvious. In the comparative aspect, we should note that the procedural mechanisms for extending such a period are provided, for example, by the criminal procedural legislation of Uzbekistan (Art. 265 of the CPC); Moldova (Art. 152 of the CPC); Lithuania (Art. 141 of the CPC); Estonia (Art. 102 of the CPC) and others[1].

Survey results: 16.7% of respondents admitted that there may be situations in which a two-month period of an inpatient FPE will not be enough to provide a complete and objective conclusion, and therefore there will be a need to extend the period of a person's stay in a psychiatric hospital. The respondents indicated 3 months as the maximum term for this.

Features of police detention of a person suffering from a mental disorder. Of particular importance in criminal proceedings is the question of the effective interaction of the police with medical workers in the field of psychiatry during the detention of a person suffering from a mental disorder. We should consider it in the analysis context of the Case of Shchiborshch and Kuzmina v. Russia [19], the main circumstances of which are as follows. Thus, 37-year-old K. Shchiborshch was an economist and author of more than 100 publications. He suffered from mental disorders that required inpatient treatment. During the aggravation of K. Shchiborshch's health (he raved and did not allow anyone to enter his apartment), his father asked the police to help hospitalize his son in a psychiatric institution. During unsuccessful attempts by the police to take him to a psychiatric hospital, K. Shchiborshch resisted, injuring several police officers with a kitchen knife, as a result of which police officers called a special unit of operational purpose to the scene for help. During the storming of the apartment K. Shchiborshch received serious injuries, with which he was taken in a coma to the hospital, where he died a few hours later. Criminal proceedings were instituted against the police officers, which were subsequently closed because it was recognized that the use of force by the police officers was in accordance with the law. However, in this case the ECHR found a violation of Art. 2 of the Convention (right to life) in part: 1) lack of planning and control of the operation of involuntary hospitalization of K. Shchiborshch; 2) evasion of an effective investigation into the event that led to the death of K. Shchiborshch. Thus, the ECHR noted that the investigating authorities did not investigate why the police acted independently, without the participation of psychiatrists, in violation of the Law on Psychiatric Care. In addition, the ECHR emphasized that the investigating authorities had considered the situation if an armed offender had acted in it, without taking into account the mental state of K. Shchiborshch (§ 258 of the Case of Shchiborshch and Kuzmina v. Russia).

The above case clearly demonstrates the special importance of adhering to the principle of cooperation between police officers and medical workers in the field of psychiatry during the detention of a person suffering from mental disorders. This principle is aimed at the joint effective implementation of these entities of two interrelated tasks from the standpoint of ensuring the rights of such a person. Thus, during the detention of persons suffering from a mental disorder, the special importance of the participation of psychiatrists is to establish psychological contact with them, which can prevent or minimize the risks of potential danger to themselves and others around them. That is, psychiatrists should provide qualified communication with persons suffering from a mental disorder in order to convince them of the need to comply with the lawful requirements of police officers. In turn, police officers must provide a security regime for the professional interaction of medical workers with a person suffering from a mental disorder, and detain the person.

Survey results: To our question to psychiatric experts "Can the participation of a psychiatrist in the police detention of a person suffering from a mental disorder help

[1] In our opinion, the extension of the term of an inpatient FPE in Ukraine may take place in accordance with Articles 197 and 199 of the CPC of Ukraine for the extension of detention (as, for example, in Lithuania).

to establish psychological contact with them and prevent or minimize the risks of potential danger to this person for themselves and others?", the answers were distributed as follows: 27.8% of respondents gave an affirmative answer; 11.1% of respondents indicated the likelihood that such participation could be effective; 61.1% gave a negative answer. Interpreting the results, it is possible to assume that the rejection of the idea by the vast majority of psychiatrists can be explained by subconscious or conscious projection on their own professional activities of the inconvenience that may entail the implementation of this idea (in particular, the need to participate in conflict situations outside a specialized psychiatric institution).

DISCUSSION

The involuntary placement of a person in a psychiatric institution has already been the subject of scientific consideration in a medical aspect (see at: Saya A., Brugnoli C., Piazzi G., Liberato D., Di Ciaccia G., Niolu C., & Siracusano A. [20]), and in law one (see at: Tijs Kooijmans and Gerben Meynen [18] and Christopher Slobogin [21]), in particular in criminal procedure (see at: Ruchina O. [22], Tsokolova O. [23]). The special vulnerability of persons suffering from mental disorders is due to the increased scientific interest in ensuring their rights in criminal proceedings. This vector of scientific research has been adopted by such authors as Peter Verbeke, Gert Vermeulen, Tom Vander Beken, Michaël Meysman [24]; Stephen J. Morse [25] and others. The issue of ensuring the rights of persons with mental disorders during criminal proceedings was also considered by the authors of this article together with Olena A. Leiba [26]. Since the use of coercion in the provision of medical care always raises the question of the proportionality of such coercion with the desired result, in this regard, we should mention the work of A. Nilsson [27]. The issue of action in the law enforcement and medical practice of Ukraine of international standards for the application of coercive measures of a medical nature was raised by Andrii V. Lapkin, Daryna P. Yevtieieva, Vladyslav V. Karelin [28]. At the same time, the review of works allows to state that at present a number of questions connected with definition of the bases and procedural order of placement of the person in a medical institution in order to conduct the FPE remains debatable. At the present stage, it is necessary to understand the compliance of national law enforcement practices with the legal positions of the ECHR and international standards in general in the context of ensuring the rights of persons for whom an inpatient FPE is appointed.

CONCLUSIONS

1. Interpreting the legal position of the ECHR in the context of placing a person in a medical institution in order to conduct the FPE, it should be noted that this measure combines both components of restriction of the right to liberty: objective element (inpatient detention) and subjective element (lack of reliable consent of the person to such stationary maintenance in order to conduct the FPE). Therefore, by its legal nature, the placement of a person in a medical institution in order to conduct the FPE is certainly a restriction of a person's right to liberty in the context of Art. 5 of the Convention.
2. The analysis of the case law of the ECHR allows us to state that the documentary basis for placing a person in a medical institution for the FPE is an expert opinion. If it is impossible to answer the questions posed during the outpatient FPE, the expert must justify the need for it in an inpatient form. At the same time, identifying the conclusion of an outpatient psychiatric examination and a medical certificate confirming the presence of a person's mental disorder is an erroneous approach, as a medical certificate cannot be a basis for the appointment of an inpatient FPE.
3. At the level of national legislation, the mechanism for extending the period of an inpatient FPE should be regulated (in the legal field of Ukraine, it may be similar to the procedure for extending the period of detention, as, for example, in Lithuania). The deadline should not exceed 3 months.
4. During the detention of a person suffering from a mental disorder, the principle of cooperation between the police and medical staff in the field of psychiatry formulated by the ECHR is of particular importance. Psychiatrists should provide qualified communication with a person suffering from a mental disorder in order to convince them of the need to comply with the lawful requirements of police officers. In turn, police officers must provide a security regime for the professional interaction of medical workers with a person suffering from a mental disorder, and detain the person.

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ORCID and contributionship:
Olga I. Tyshchenko: 0000-0001-8872-799X [A, B, C]
Ivan A. Titko: 0000-0003-4126-6967 [B, D, E, F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Ivan A. Titko
Poltava Law Institute of Yaroslav Mudryi National Law University
5 Pervomaisky Av., 36000 Poltava, Ukraine
tel: +380975150748
e-mail: titko.iv@gmail.com

Received: 22.04.2020
Accepted: 05.08.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

BASIC PRINCIPLES OF BEHAVIORAL ECONOMICS AND PROSPECTS FOR THEIR APPLICATION IN THE PUBLIC HEALTH SYSTEM

DOI: 10.36740/WLek202009225

Lesia A. Rudenko[1], Vladyslav A. Smiianov[2], Olha I. Smiianova[2]
[1]ALUNA PUBLISHING HOUSE, KONSTANCIN-JEZIORNA, POLAND
[2]SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Behavioral economics is a branch of economic theory that studies the influence of psychological factors on people's decisions in various life situations. At the same time, much attention is paid to situations where people behave differently than predicted by classical economic theory with its assumption of rationality and selfishness. Interesting possibility of application of behavioral economic in various spheres of human life and society, for example, reforms introducing, insurance system, public health and medicine (healthy living, disease prevention, following-up to the doctor's recommendations, improving the quality of care, etc.).

KEY WORDS: public health, behavioral economics, nudge, framing, bounded rationality effect

Wiad Lek. 2020;73(9 p. II):2036-2040

INTRODUCTION

The problem of determining the role of human in economy has always been relevant. For a long time there was a notion, first presented by Adam Smith, about «homo economicus» (economic man) - a rational egoist who knows exactly his interests and needs and always makes economically correct decisions according to them [1]. Such a person can be called "economical" person. However, over time, some inconsistencies began to emerge in practice and it turned out that human behavior is not always rational, and often quite opposite to rational. We will call such people «behavioral». This became a new subject of study for many economists in the 50-60s of the 20th century. The new direction was called «behavioral economics» [2, 3].

Behavioral economics (BE) is the science that studies actual behavior of economic agents and corresponding psychological factors that influence economic behavior [2]. Behavioral economics is a branch of economic theory that studies the influence of psychological factors on people's decisions in various life situations [3]. At the same time, much attention is paid to situations where people behave differently than predicted by classical economic theory with its assumption of rationality and selfishness.

THE AIM

Introduction to the basic principles of behavioral economics and prospects for their application in the public health system.

MATERIALS AND METHODS

In the course of the research the bibliographic, bibliosemantic method, the method of system analysis and medical-statistical method. An analysis of foreign literature was conducted of behavioral economics. Also, an analysia of the study on the effectiveness of the reminding system for patients with hypertension, who were registered with family doctors, the study involved 2019 patients with hypertension.

REVIEW AND DISCUSSION

The founders of BE theory are considered to be an American economist Herbert Simon and a sociologist Daniel Kahneman, who received the Nobel Prize in Economics in 2002. In 2017, Richard Thaler was awarded the Nobel Prize for his contribution to the development of BE theory [2, 3].

What`s interesting is Thaler's important contribution is not only the development of behavioral economic theory, but also possibility of its application in various spheres of human life and society. For example, policy, reforms introducing, insurance system, public health and medicine (healthy living, disease prevention, following-up to the doctor's recommendations, improving the quality of care, etc.). People or institutions that are responsible for organizing the context in which people make decisions are called «architects of choice.» This can be a doctor who tells the patient about alternative treatments, or information institutions that influence people's behavior. Each health care specialist must be the «architect of choice» him- or herself.

R. Thaler unites his supporters under the banner of libertarian paternalism (LP). The libertarian component of

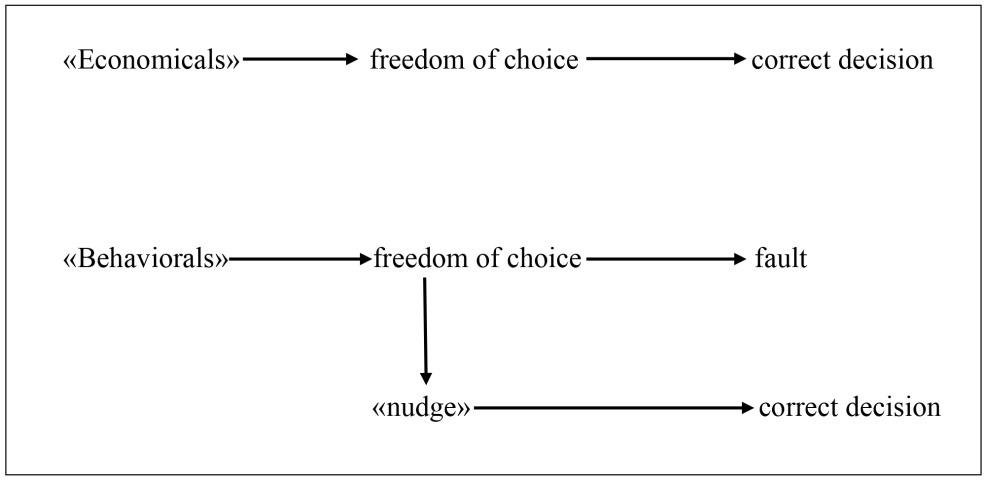

Fig. 1. Decision scheme.

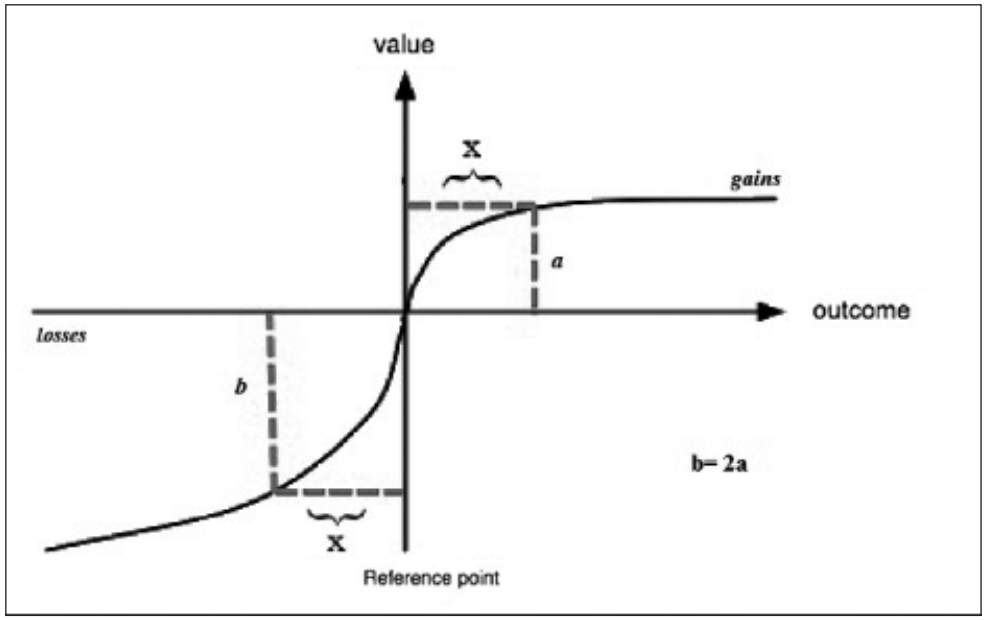

Fig. 2. Loss aversion.

this strategy clearly states that, generaly, people should be free to do what they like and have freedom of choice. The paternalistic component determines the legitimate influence on people's behavior in such a way as directing their choices in areas that can improve their lives [2, 3]. LP is a relatively weak, mild, and unobtrusive type of paternalism because choice is not blocked or overburdened. If people want to smoke cigarettes, eat sweets, not to worry about their health, LP will not force them to do the opposite, but rather will carefully try to guide people in areas that can improve their lives by "pushing" them.

Richard Thaler pays special attention to the motives that stimulate person to choose, which he called «nudge» (push) [4]. A push or a nudge is any aspect that changes people's behavior in a predictable way without forbidding any options [5]. Nudges are not orders. Placing fruits at eye level in the canteen is a nudge, and banning junk food is not.

"Behavioral" people in opposite to the "economical" make mistakes predictably (Fig. 1). Small and clearly insignificant details can be a nudge and create a huge impact on people's behavior. An interesting example of this principle is men's restrooms at Amsterdam Airport. The airport administration suggested drawing a fly in each urinal. It turned out reducing the cost of cleaning men's restrooms up to 80% [2, 3].

As noted, classical economic theory considers perswon as rational, choosing only the best option for himself. But people aren't really like that at all. They are not homo economicus, but homo sapiens ("behaviorals"). Unfortunately, ordinary people often behave irrationally and incorrectly, even for their own health. They smoke, drink alcohol, eat poorly, suffer from overweight, keep unhealthy lifestyles, and do not follow a doctor's prescription, although most are well aware that it increases the risk of cardiovascular diseases, diabetes, cancer and can lead to premature death. Sociological research shows that most of behavioral people would like to get rid of bad habits and keep a healthy lifestyle. They need adequate nudges.

Psychologists and neurobiologists note the differences between two types of thinking: one is intuitive and automatic, and the other is reflective and rational. The automatic system is an intuitive reaction, and the reflective system is a conscious thought. The automatic system is fast, uncontrolled, unconscious, receives information from instincts,

not related to comprehension. When a person dodges the ball, he uses an automatic system. The reflective system is slower, controlled, conscious, does not keep up with the automatic one. If people can rely on their automatic system without making a mistake, their lives will be much better and longer. Herbert Simon presented the term «limited rationality», when people often make decisions quickly based on automatic system to meet their needs, and that may not necessarily be the best option [2, 3, 6]. Behavioral economists encourage "choice architects" to participate in creating nudges for quick solutions (automatic system). Sunstein and Thaler's experiment of placing healthy food in school canteens at eye level and in the front row so that children make the right choice automatically is well known.

Consider some typical examples of human behavior.

Gains and losses. People do not like to lose. They suffer more from losing something than they will enjoy gaining it. Many experiments have shown that this ratio equals a difference in 2.25 - 2.5 times. This conclusion is called "loss aversion" (LA) [2, 3, 6] (Fig. 2). LA encourages inertia, i.e. a strong desire to maintain the state of affairs that exists today. LA plays the role of a kind of cognitive impulse that forces us to change nothing, even if the changes are in our favor.

For many reasons, people show a general tendency to follow the state of affairs that exists today. This phenomenon, which William Samuelson and Richard Zeckhauser (1988) called the «status-quo bias» occurs quite often [2]. For example, when you buy a new mobile phone, you have to set up a number of options. For each of these options, the manufacturer has set one default option. Research shows that no matter what kind default options are like, most people don't change them. Two important conclusions can be drawn from these studies. The first is never underestimate the force of inertia. Second, this force can be used. There is another example of using the *default option*. In the Netherlands, only 27.5% of the population agreed to be organ donors. In neighboring Belgium, organs are allowed to be taken from all people except those who have refused to donate (presumption of consent). As a result, 98% of Belgians are donors. The effect of a well-chosen default option is just one example of a gentle nudge action.

Unwarranted optimism and overconfidence. Behavioral people usually think that they are much less likely than others to lose their jobs, have a heart attack, or get cancer. Drug addicts and gays underestimate the risk of contracting AIDS. Smokers are aware of the statistical risks, but generally believe that lung cancer and cardiovascular diseases are more commonly diagnosed in non-smokers. The wild popularity of lotteries is due to unwarranted optimism. Unwarranted optimism is a common feature of human life [2, 3]. If people take risks because of unwarranted optimism, they can be helped by nudge. To do this, one can simply remind them of the real risks and tragic results and their optimism will fade a bit.

Framing is the dependence of decision-making on the submission of information. A person's choice often depends on how the problem is formulated. For example, if doctor says that out of a hundred operated cancer patients, ten die within five years, the patient is more likely to refuse surgery. And if the doctor says that under the same conditions, out of a hundred patients, ninety will live for five years, the decision on surgery may be different [7]. This means that frames are powerful nudges and it is needed to be very careful with them, especially in medical practice. Examples of framing: negative information carries negative associations, and positive – vice versa (the effect of our television - a constant negative, stress, depression, irritation). Example: refusal of vaccination [8].

Mechanism of social forces. Social forces are one of the most effective ways of nudge (fortunately or not). For example, in our city more and more dog owners take them for a walk, not forgetting to pick up cellophane bags. They do so by the example of others, despite the fact that there are no fines for walk without further cleaning. There are two types of social forces: information and social pressure/impact. Most people worry what others will think about them, so they are able to follow the crowd to win their favor or avoid their condemnation [9]. For example: students' academic performance is significantly influenced by their environment (classmates or roommates). Obesity, smoking, alcohol consumption – all bad examples are catching. If your best friends are abusing this, then you are more likely to start abusing it. Visual feedback enhances the impact of social forces. People tend to do what others do, especially when they know the information will be public. The mechanism of social influence is very often used in economics, finance, politics. In our opinion, its use in medicine, disease prevention, formation of a healthy way of life is perspective.

Marketers, aware of the power of social forces, often emphasize that most people choose their product and switch from another brand (which became out-of date) to that they present [8, 10]. They nudge people, talking about the modern preferences of the majority. If such information is also provided in digital support, the effect of such nudge is enhanced. Given the possibility of changing behavior by emphasizing statistical reality, an anti-smoking experiment was conducted at Montana college. The media claimed that «most of students (70%) do not smoke.» It was proved that such a strategy significantly increased the effectiveness of social perception and achieved a statistically significant reduction in smoking.

Feedback. The best way to help people improve their performance is to provide them with feedback. A well-organized feedback system encourages a person to become an active participant, which in turn increases the efficiency of the process [10]. This approach can be especially relevant and promising in public health and medicine (maintaining a healthy lifestyle, disease prevention, following a doctor's appointment, etc.).

Priming. It is often possible to correct certain behaviors of people by invisibly getting certain information into the brain. Sometimes the slightest hint of an idea can evoke a certain association, which in turn can stimulate action. Such primes (stimuli) occur in social situations and can be

powerful nudges [2, 3, 5]. For example, when sociologists ask respondents what they are going to do, they are more likely to act on their answers. This effect (simple measurement effect) can be enhanced by asking when and how they plan to do it. When Yale University students were invited to get vaccinated after a lecture on the risks of tetanus, only 3% did it. Another group of students was asked to choose a convenient day and time of vaccination, 28% of students did it, which is nine times more.

Forgetfulness. Nobody likes to forget something important. However, in just one day, the human brain has to process so much information that some of it is not stored. In our lives, managing this brain function can greatly facilitate the work of physicians. After all, according to statistics, the main problem of untimely (irregular) medication is forgetfulness. Physiologically, the brain normally perceives and processes reminders using an automatic system without additional effort.

The Department of Public Health of Sumy State University conducted a study on the effectiveness of the system of reminding patients with hypertension (AH), who were registered with family doctors in Sumy. The analysis of the research results showed its high efficiency and prospects [11].

The study involved 2019 patients (men - 29.2%, women - 70.8%). At the first stage, a survey of patients with hypertension was conducted. The results of monitoring patients with hypertension showed that:

- 97.2% of patients are aware, according to their words, about prevention, the course of the disease and consequences of hypertension;
- 98.4% of respondents have their own pressure gauge to measure pressure;
- 37.1% irregularly monitor their pressure;
- 8.3% of patients did not measure pressure at all during current year;
- 52.3% of respondents take medicines irregularly, 20% do not take medication at all;
- 32% of respondents did not visit a doctor for prophylactic purposes;
- the main reason for irregular medication and blood pressure control patients indicate as forgetfulness (48.3% among all patients);
- Almost all respondents noted that they were prescribed free prescriptions for antihypertensive drugs, but 37.4% of them did not use them for their intended purpose. The reason « I forget» occured in 66.7%.

Basing on the results of the audit, a proposal for information and technological reminders to patients with SMS-messages about need to control blood pressure and medication was developed and implemented [11].

A year later, a re-audit showed the effectiveness of the implemented proposal:

- the number of patients with target pressure increased from 14% to 39%;
- the number of hypertensive crises decreased by 17.8%;
- the number of patients who began to monitor blood pressure regularly and take medication increased by 31% [11].

Prospective risk assessment. This is a biased risks` assessment, when people can easily imagine them from a nuclear power plant accident, tsunami, earthquake, plane crash, and so on [12]. They mistakenly think these risks are high for them. And for the risks of stroke, heart attack, asthma attack people give low estimates, even if they occur much more often (the difference is up to twenty times the value). In all mentioned examples, the automatic system reacts sharply to risk without resorting to any tables with boring statistics. A good way to bring people back to reality is to constantly remind them of the real state of affairs.

CONCLUSIONS

1. People are prone to the perception of impulses (they are «nudge-receptive»). Even the most important decisions in life can be influenced by the ways and methods of behavioral economics.
2. During all life, a person is rarely affected by only one of the mechanisms of BE, but mainly by combination and interaction of several factors that are in synergy with each other. It is still up to researchers to study these interactions and connections.
3. Today, we see that existing methods of health education have ceased to be effective (morbidity and mortality from chronic diseases are increasing, the number of vaccinated is decreasing, etc.). In our opinion, it is necessary to change the paradigm in this important part of public health and look closely at developments in the field of BE. The proposed theory of «nudge» can open a new page in prevention of many diseases and promotion of a healthy lifestyle.

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ORCID and contributionship:
Lesia A. Rudenko: 0000-0003-0556-8263 [D, E, F]
Vladyslav A. Smiianov: 0000-0002-4240-5968 [A, B, D, F]
Olha I. Smiianova: 0000-0001-5823-924X [B, E, F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Vladyslav A. Smiianov
Sumy State University
Praci Str., 3, 40000, Sumy, Ukraine
tel: +380507713008
e-mail: vladlor60@ukr.net

Received: 14.04.2020
Accepted: 03.08.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

KIDNEY STONE DISEASE WITH SPECIAL REGARD TO DRUG-INDUCED KIDNEY STONES – A CONTEMPORARY SYNOPSIS

DOI: 10.36740/WLek202009226

Łukasz Dobrek
DEPARTMENT OF CLINICAL PHARMACOLOGY, WROCLAW MEDICAL UNIVERSITY, WROCLAW, POLAND

ABSTRACT

Kidney stone disease (nephrolithiasis; urolithiasis) is a clinical entity with long-term course and recurrence, primarily affecting mature and ageing men, involving the formation and presence of urinary stones in the kidneys and urinary tract. The pathogenesis of this disorder is complex and still not fully understood. A rare, potentially modifiable, form of kidney stone disease takes the form of drug-induced urinary stones.

The aim of the review was a brief description of the classification and pathophysiology of kidney stone disease, along with the short characteristics of drug-induced urinary stones. This type of stones is formed as a result of crystallisation in the kidneys and urinary tract of sparingly soluble drugs and their metabolites, or as a result of metabolic changes caused by drugs, predestinating the development of stones containing endogenous compounds.

Conclusion: Therefore, during treatment with the use of drugs with high lithogenic potential, the safety of pharmacotherapy should be monitored in the context of its increased risk of developing urinary stones.

KEY WORDS: kidney stones, urolithiasis, nephrolithiasis, drugs, adverse drug reaction

Wiad Lek. 2020;73(9 p. II):2042-2055

INTRODUCTION

Urinary lithiasis is as old as humanity – the first mention of urinary stones comes from the ancient times and the first stones were identified in Egyptian mummies. In 1901, the English archaeologist E. Smith, who performed his excavation works in El Amrah in Egypt, found a bladder stone from a 4500–5000-year-old mummy [1]. Documented written notes regarding urolithiasis and its management date back to 3200–1200 BC [2]. The first surgical descriptions of "cutting for the stone" were given by a surgeon who lived in ancient India – Sushruta, around 600 BC. He was the author of the book Sushruta Samhita, in which he characterised about 300 surgical procedures, including perineal lithotomy [1]. Thus, mankind has known kidney stone disease since its inception and the disorder invariably accompanies our civilization through the centuries.

Nowadays, kidney stone disease (also referred to as nephrolithiasis or urolithiasis) is a relatively common clinical entity and the estimates indicate that the general prevalence of the disease vary between 1 and even 20% [3]. The overall incidence of kidney stone formation, however, ranges in different parts of the world. In an adult population, the risk of kidney stone development seems to be lower in Asia (1–5%; mostly Pakistan, India, Thailand, Indonesia, the Philippines) than in Europe (5–9%; especially the British Isles, Scandinavian countries, Central Europe, Mediterranean countries), Canada (12%) and USA (13%). The highest number of patients suffering from renal stones is reported in Middle Eastern countries (e.g. about 20% in Saudi Arabia and in Sudan, Egypt, the United Arab Emirates, Iran) [4,5], probably because of the hot climate and increased risk of dehydration, which is an important environmental factor of kidney stone development. Kidney stone disease affects all ages, sexes and races but its incidence rate is higher in ageing men (male/female ratio is 2/1) and only 1–2% of urinary lithiasis patients are children [4].

A characteristic feature of kidney stone disease is its chronicity. The disease is characterised by high recurrence. Without any management, in about half of all patients, the next episode of the disturbance is observed over the course of ten years. Moreover, the recurrence rate is approximately 10% at 1 year and 33%–40% at 5 years [5,6].

When untreated or incorrectly treated, recurrent kidney stone disease is associated with progressive kidney damage and increased risk of chronic kidney disease development. Renal stones account for 2–3% of end-stage renal cases, mostly if nephrolithiasis is associated with nephrocalcinosis [7]. Other data estimate that this disease is even the cause of terminal chronic kidney disease requiring renal replacement therapy in 5% of European patients [8].

To sum up, kidney stone disease is a significant health problem. One of the causes of the disease, although rare, are drugs used in the pharmacotherapy of multiple diseases.

THE AIM

The aim of this paper was to discuss the basic issues of drug-induced kidney stones against the background of the general pathophysiological premises of nephrolithiasis.

Table I. The basic characteristic of urinary stones [3,10].

Chemical name	Common mineral name	Chemical formula	Shape of crystals in light microscopy	General etiology	X-ray feature
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4*H_2O$	Dumbbell-like; Biconcave disks	Non-infectious	Radiopaque
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4*2H_2O$	Bipyramids; Envelope-like	Non-infectious	Radiopaque
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6*(OH)_2$		Non-infectious	Radiopaque
Tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$		Non-infectious	Radiopaque
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$		Non-infectious	Poor radiopacity
Calcium carbonate	Aragonite	$CaCO_3$	Large spheroids with radial striations or smaller crystals with round to ovoid shapes	Non-infectious	Poor radiopacity
Uric acid	Uricite	$C_5H_4N_4O_3$	Rectangular or rhomboidal	Non-infectious	Radiolucent
Ammonium urate		$NH_4C_5H_3N_4O_3$	Spherical bodies with irregular protrusions ("thorn-apples")	Infectious	Radiolucent
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4*6H_2O$	Coffin-lid	Infectious	Poor radiopacity
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4PO_4*H_2O$		Infectious	Poor radiopacity
Cystine		C6H12N2O4S2	Hexagonal	Genetic	Poor radiopacity
Xanthine		C5H4N4O2		Genetic	Radiolucent
2,8-Dihydroxyadenine		C5H5N5O2		Genetic	Radiolucent
Other rare calculi (e.g. proteins, cholesterol, bilirubin, melamine, drug stones, foreign body calculi)			e.g. bilirubin - needle-like to granular crystals that are yellow in color	Other, complex mechanisms	Radiolucent (mostly)

MATERIALS AND METHODS

Narrative full-text reviews published in the English language were search in PubMed-NCBI and Google Scholar databases. The various applied search terms included: "kidney stone disease", "nephrolithiasis", "urolithiasis", "kidney stone", "renal stone", "drug-induced kidney stones", "drug-induced renal stones", "drug-induced nephrolithiasis", "drug-induced urolithiasis".

Published articles on or after 2000, which were available as free full texts on the public domain were selected during the performed query.

REVIEW AND DISCUSSION

TYPES OF KIDNEY STONES

Urinary stones can be classified according to chemical composition (mineralogy), the overall aetiology of formation, size, location or X-ray features [3]. The stone composition indirectly determines the size and shape of urinary stones and is an important premise for management decisions. A brief summary of individual stone types is given in Table I.

Based on the above-mentioned chemical composition, five main types of stones can be classified: calcium, struvite or magnesium ammonium phosphate, uric acid or urate, cystine and rare stones (including drug-induced ones). The above-listed stones contain mineral or small organic compounds, which form crystals, while the matrix as a non-crystalline phase acts as a template participating in the assembly of urinary deposits. The organic matrix is composed of glycosaminoglycans, cell membrane lipids, carbohydrates and some proteins [7].

Calcium stones account for about 80% of all urinary stones (70% of all urinary stones are composed of calcium oxalate and 10% include calcium phosphate or other calcium-containing deposits). The factors responsible for calcium stone formation are complex and mainly involve: low urine volume, hypercalcuria (due to enhanced renal resorption, intestinal absorption or metabolic calcium turnover disorders), hyperoxaluria, hypocitraturia, hypomagnesuria, hyperuricosuria or hipercystinuria. Urinary pH of 5.0–6.5 favours calcium oxalate stone development, whereas pH greater than 7.5 is a causative agent of calcium

Table II. Inhibitors and promoters of urinary stones development [7].

Stage of lithogenesis	Inhibitors	Promoters
Nucleation	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin glycosaminoglycans	Tamm-Horsfall protein (uromodulin) albumin collagen
Crystal growth	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin histone-lysine N methyltransferase alpha – 2HS glycoprotein chondroitin sulphate heparin sulphate human urinary trefoil factor 1 glycosaminoglycans citrate pyrophosphate magnesium	alpha-defensin myeloperoxidase histone H1B
Aggregation	nephrocalcin osteopontin albumin urinary prothrombin fragment-1 alpha-1-microglobulin bikunin fibronectin	alpha-defensin myeloperoxidase
Retention	osteopontin bikunin crytal adhesion inhibitor fibronectin glycosaminoglycans	nucleolin hyaluronic acid monocyte chemoattractant protein-1 annexin II antigen CD44

phosphate deposit growth [5, 7, 10, 11]. As a side note, it should be mentioned that, although calcium stones, contrary to struvite ones, are regarded as non-infectious, there are some reports suggesting that nanobacteria may contribute to the formation of a calcium phosphate shell, serving as a crystallisation centre for those stones [11].

Struvite stones form about 10–15% of all cases of kidney stone disease and their development is highly associated with chronic urinary tract infection caused by urease-producing bacteria (*Proteus mirabilis, Klebsiella pneumonia, Pseudomonas aeruginosa, Ureoplasma urealyticum, Escherichia coli* and *Enterobacter*). In more than half of all urease-producing infections, Proteus mirabilis was found to be a causative factor. Bacterial urease splits urea into ammonia and carbon dioxide with subsequent elevation of urinary pH. Alkaline urine decreases the solubility of phosphates that precipitate to insoluble ammonium products and usually take the form of large "staghorn" stones [5, 7, 8, 10, 11].

Uric acid stones or urate constitute about 5–10% of all urinary stones. They develop mostly as a result of hyperuricosuria due to the elevation in endogenous uric acid production and its excretion into urine. This occurs in high purines intake (diet rich in meat and fish containing animal proteins) and the precipitation of uric acid occurs in low urinary pH (uric acid is poorly soluble in acidic urine with pH about 5.5 or less). Those stones contain uric acid only or additional calcium [5, 7, 8, 10].

Cystine stones account for less than 1–2% of all cases. They are conditioned by genetic disturbances manifesting by hypercystinuria. This is associated with an autosomal recessive disorder due to the rBAT gene attributed to chromosome 2 deficiency, resulting in abnormal renal tubular reabsorption of cystine, ornithine, lysine and arginine. These types of stone are usually large and bilateral [5, 7, 8, 10].

According to the general aetiology, one can distinguish infectious and non-infectious stones, those caused by genetic defects and those induced as a result of adverse drug reactions [3].

In terms of size, urinary stones can measure up to 5, 10, 20 or above 20 mm, at their largest [3]. Deposits smaller than 5mm, after several weeks of conservative treatment most often pass spontaneously through the urinary tract and are excreted. Larger stones require specialist treatment and urological procedures for removal, while stones above 10 mm are unlikely to be expulsed unaided [6]. In terms of the general location of urinary stones, these may be located inside the kidney (in the upper, middle or lower calyxes or in the renal pelvis) and/or in the urinary tract (in the upper, middle or distal urether, in the urinary bladder or the urethra) [3]. The special term "staghorn renal stones"

Table III. The most common drug-induced urinary stones [25-28].

Class of drugs	Drugs examples	Primary stone composition	Rationale for stone development
Drug-containing stones			
Sulfonamides	sulfadiazine	sulfadiazine, N-acetylsulfadiazine	The basic premises for these types of stones development are: (1) The long-term treatment involving the administration of high doses of drug excreted by the kidney; (2) The administered drug and its metabolites are poorly soluble in urine; (3) There is the co-existence of the patient-dependent risk factors for the development of urinary stones.
	sulfaguanidine	N,N-diacetylsulfaguanidine	
	sulfamethoxazole	N-acetylsulfamethoxazole	
	sulfasalazine	N-acetylsulfapyridinine	
Antibiotics	aminopenicillins	ampicillin trihydrate amoxicillin trihydrate	
	cephalosporins	calcium ceftriaxonate	
Quinolones	pipemidic acid	pipemidic acid	
	ciprofloxacin	ciprofloxacin magnesium salt	
	norfloxacin	norfloxacin magnesium salt	
Other antibacterial drugs	nitrofurantoin	nitrofurantoin	
Protease inhibitors	indinavir	indinavir monohydrate	
	nelfinavir	nelfinavir	
	atazanavir	atazanavir	
Antacids	magnesium trisilicate	amorphous silica	
	aluminium hydroxide	aluminium magnesium potassium urate	
Various drugs	triamterene	triamterene, hydroxytriamterene sulfate	
	allopurinol	oxypurinol	
	ephedrine	ephedrine, norephedrine, pseudoephedrine	
	acyclovir	acyclovir	
	methotrexate	methotrexate, 7-hydroxymethotrexate	
Drug-induced "metabolic stones"			
Calcium-containing supplements	many commercially available	calcium oxalate, calcium phosphate	These drugs enhance an intestinal calcium absorption, leading to the hypercalcemia and the hypercalciuric state.
Vitamin D-containing supplements	many commercially available		
Loop diuretics	furosemide		
Anhydrase inhibitors	acetazolamide	calcium phosphates, mainly carbapatite	These drugs inhibit bicarbonate reabsorption and hydrogen ion excretion in proximal tubules, leading to systemic metabolic acidosis, an increase in urinary pH and decrease of urinary citrates.
	zonisamide		
	topiramate		
Laxative drugs (when abused)	hyperosmotic or stimulant agents	ammonium urate, uric acid, calcium oxalate	These drugs, when abused, cause an increased gastrointestinal fluid and potassium loss and low urinary output. The potassium depletion contributes to intracellular acidosis compensated by renal ammoniagenesis enhancement in kidney proximal tubules and increased citrate reabsorption, potentiated by increased expression of the H+/K+ activity in the distal tubules.
Corticosteroids	cortisol	calcium oxalate, calcium phosphate	These drugs promote the release of calcium from bones and lead to the hypercalcuria and hyperphosphaturia state.
Ascorbic acid (vitamin C)	many commercially available of dietary supplements	calcium oxalate	The excess of vitamin C is metabolized to oxalates and it increases the urinary oxalates excretion. Moreover, high doses of vitamin C also contribute to urinary acidification.
Xanthine oxidase inhibitors	allopurinol	xanthine, oxypurinol	The drug inhibits the biotransformation of hypoxanthine into xanthine and final synthesis of uric acid, leading to the formation of xanthine-containing purine stones.
Uricosuric drugs	benzbromarone probenecid	uric acid	These drugs reduce hyperuricemia by enhancing urinary uric acid excretion, leading to the formation of uric acid-containing purine stones.

refers to the massive kidney stones that fill the renal pelvis and at least one of the renal calyces [9]. The comparison of urinary stones depends on their chemical composition. In kidney-urether-bladder radiography, radiopaque (calcium oxalate, calcium phosphates), those characterised by poor radiopacity (magnesium ammonium phosphate, apatite, cysteine) and radiolucent (uric acid, ammonium urate, drug-induced) urinary stones can be distinguished [3].

THE RISK FACTORS OF URINARY STONE FORMATION

The main factors determining urinary stone development can be divided into individual and environmental. The first group includes sex, race, age, inheritance, genetic features and individual predisposing diseases. As already mentioned above, kidney stone disease is more common in ageing men, usually manifesting itself for the first time in patients aged 20–50 [7]. Genetic predisposition must be taken into account in a patient with a family history of stones and in the diagnosis of renal tubular acidosis, cystinuria, Barret's syndrome or genetic monogenic diseases. Among the diseases predisposing to the development of urinary stones, both metabolic (hypercalcuria, hypocitraturia, hyperoxaluria, hyperuricosuria and a history of gout) and anatomical (medullary sponge kidney, ureteropelvic junction stenosis, pyeloureteral duplication, polycystic renal disease and horseshoe kidney) disorders should be listed. Other diseases contributing to urinary stone development are: hyperparathyroidism, hypertension, obesity, inflammatory bowel diseases or other intestinal malabsorption states and recurrent urinary tract infections. Environmental factors involve climate change (global warming) and seasonal variations (higher prevalence of urinary stones in summer rather than winter), socio-economic conditions and associated lifestyle, and dietary habits or low water intake causing dehydration and subsequent low urine output [4, 7, 10]. Diet is a very important risk factor of kidney stone disease. Lack of drinking water with an excessive intake of animal proteins, salt and vitamin D with reduced content of citrate, fibre and potassium in the diet are considered to be the main abnormalities leading to urinary stone formation. Studies also suggest that high intake of carbohydrate-rich food and less physical activity are directly proportional to kidney stone disease development. Conversely, regular consumption of water (up to 2.5–3 litres per day, unless otherwise indicated), fruit and vegetables (except green leafy ones containing a higher amount of oxalates) and maintaining proper physical activity are the most important preventive factors [12].

THE PATHOPHYSIOLOGY OF KIDNEY STONES. MECHANISMS OF URINARY STONE FORMATION

The pathophysiology of kidney stone disease (nephrolithiasis, urolithiasis) is complex and still not fully understood. The general pathophysiological premises of urinary stone formation assume three main disturbances: (1) an excessive urinary concentration of some compounds, exceeding their solubility in the urine, (2) an imbalance between promoters and inhibitors of precipitation, and (3) urothelial abnormalities allowing an attachment and subsequent growth of the rising urinary deposits [5]. There are a few "milestone" points in the complex pathophysiological cascade of urinary stone development.

The initiation phase of the process is nucleation, followed by a stage of crystal growth with their subsequent aggregation and retention on the surface of the renal tubules. Nucleation can be described as a phase change of dissolved mineral compounds into a solid, with the formation of a nucleus, also termed nidus [7]. This phenomenon is observed in a super-saturation solution that contains more of the compounds that can be dissolved in the solvent under normal circumstances. Nucleation can be either homogeneous (occurring spontaneously in an unstable zone of supersaturation when the concentration of two ions exceeds their saturation point in the solution) or heterogeneous (taking place at a lower degree of saturation in the presence of nucleating agents in urine – promoters of nucleation, such as exfoliated epithelial cells, urinary casts, red blood cells, mucopolysaccharides etc.). The promoters form a surface on which precipitation may take place, which reduces the energy necessary for crystallisation [5, 11]. The homogeneous nucleation mechanism is consistent with the general hypothesis of the "free particles", while the heterogeneous one meets the criteria of the "fixed particles" concept, which is also often mentioned in the literature [13].

In the second step, the microcrystals continue the oriented overgrowth on to a substrate crystalline lattice ("epitaxy"). Stone growth is accomplished through aggregation of the preformed crystals or secondary nucleation of the crystal on the matrix [7]. The process depends on urinary pH, the physicochemical properties of the crystallisation base material or the molecular size and shape of the precipitated compounds [5].

Aggregation is a process of binding the adjacent crystal nuclei to each other and forming larger particles due to the existence of small interparticle attractive forces conducive to aggregation [5].

The final step is the association and fixation of the crystals in the renal tubules cell lining. Thus, the retention phase consists in the interactions between the developing crystals and epithelial cells. Those interactions result in the movement of the formed and growing nidus from the basolateral cellular region and its anchoring into the basement membrane. Some of the crystals are digested and phagocytosed by locally resident macrophages or they are subjected to endocytosis with subsequent lysosomal degradation. This also leads to an increase in oxidative stress, and ultimately to damage of the renal tubules [5, 7]. This phenomenon impairs the possibility of the cellular elimination of developing crystals and allows their further growth. Finally, the formed deposits may detach from the kidney tissue and may be passed through the urinary tract, although the factors determining the passage of the stone to the urinary tract remain unknown.

At each of stage of the formation of urinary stones, the urinary stone matrix protein modulators play an important role, acting as inhibitors or promoters of a given phenomenon. Some are listed in Table II. Hence, it can also be concluded that the pathogenesis of urinary stones is the result of the deficiency of inhibitor action accompanied by the over-expression of the promoters.

KIDNEY STONES SYMPTOMS, DIAGNOSIS AND MANAGEMENT

The symptomatology and management of kidney stone disease is dependent mainly on the size and location of the urinary stones and the presence of a possible associated urinary tract infection. Stones smaller than 5 mm are likely to pass spontaneously through the urinary tract and patients require careful observation, hydration and pain treatment. Analgesics exerting additional anti-inflammatory effect used in renal colic include metamizole or, alternatively, depending on gastrointestinal and cardiovascular risk factors, diclofenac, indomethacin or ibuprofen. Opiates – morphine, pethidine, pentazocine, tramadol are regarded base drugs of second choice or they are administered to patients suffering from severe pain, uncontrolled by non-opioid analgesics [3]. During the passage of the stone through the urinary tract, renal colic symptoms present themselves. Renal colic is a severe, cramping pain evoked by the movement of a stone through the urinary tract, which is augmented by the ureteral spasm and the possible obstruction; thus, it is also treated with spasmolytic agents, such as papaverine, drotaverine, hyoscine or oxyphenonium, administered in addition to analgesics. Pain originates in the flank area and spreads downward into the genital region when the stone reaches the distal ureter. It is usually not related to body position and is accompanied by nausea, vomiting and macro- or at least micro-hematuria and often bladder overactivity symptoms (sensation of urinary frequency and urgency) [6].

Stones larger than 5 mm are mostly treated with interventional procedures. A medical expulsive therapy (MET) seems to be effective in patients who are amenable to conservative management, with distal ureteral stones > 5 mm. MET includes the administration of alpha-1-blockers (tamsulosin), calcium channel inhibitors (nifedipine) or phosphodiesterase-5-inhibitors (tadalafil). Patients treated with those agents (with the superiority of tamsulosin) exhibit fewer colic episodes compared to untreated ones [3]. Massive stones that bilaterally block the flow of urine can be a pathophysiological cause of the development of acute kidney injury and failure, with anuria and hypercreatinemia. Long-term consequences of the urinary stones involve the development of several complications, e.g. hydronephrosis or obstructive nephropathy even leading to chronic kidney disease.

The chronic treatment of kidney stone disease includes preventive methods and pharmacological agents with/or without surgical treatment. Regardless of the aetiology, the most important preventive treatment consists of hydration to reduce urine supersaturation and to maintain a urinary output of at least 2 L/day. The patient is also advised to restrict daily intake of animal proteins [14]. Pharmacological intervention involves the administration of herbal medicine containing terpenes and essential oils (e.g. Rowatinex), potassium citrate (causing a significant urinary pH increase) or thiazide diuretics, which are considered to be effective hypocalciuric agents due to their contribution to enhanced calcium reabsorption in the distal tubules. Acetohydroxamic acid reversely inhibits bacterial urease; thus, it is administrated in patients with urea-splitting bacterial infections. Urinary tract infections require treatment with antibacterial chemotherapeutics. In cystine stones, tiopronin is used to reduce urinary cystine concentration by forming a water soluble mixed disulfide complex. Surgical procedures include extracorporeal shockwave lithotripsy (ESWL), ureteroscopy or percutaneous nephrolithotomy [3, 10, 15]. There are also reports of the beneficial effects of using herbs that seems to be the safest and most inexpensive treatment; however, this requires time for the beneficial therapeutic effects to become apparent. In many countries, there are different experiences with the use of various species of herbs, including those that are often endemic only in given areas and, for this reason, they are part of traditional Chinese or Indian medicine. One can also list here, however, some plants more widely available in Europe, such as *Trigonella foenum-graecum, Origanum vulgare, Berberis vulgaris, Ammi visnaga, Oenothera biennis, Rubia tinctorum, Rosa canina, Punica granatum* and others [16, 17].

The diagnosis of urinary stones is based on both laboratory testing and imaging studies. Blood tests usually measure creatinine, urea, uric acid and electrolytes. In urine samples, the presence of red and white blood cells, nitrates and pH are determined. The microscopic assessment of urinary sediments and casts is also performed. The evaluation of chemical composition is crucial for further medical treatment and the patient is instructed to collect urine and excreted deposits for examination during stone evacuation [3, 10]. There are also precise physical methods – X-ray diffraction and Fourier transform infrared spectroscopy – enabling the identification of each chemical constituent of the urinary stone with semi-quantitative evaluation of their proportions [18]. Imaging studies for urinary stones include: ultrasonography, radiography of the kidneys, ureters and bladder (KUB), computerised tomography (CT) and magnetic resonance imaging (MRI). Ultrasound is often the first-line imaging modality due to its advantages – it is not expensive, it is portable and ubiquitous, and does not expose patients to any radiation. Moreover, it is able to detect some complications of kidney stone disease, such as ureteral dilation, peri-renal fluid or hydronephrosis. Conversely, ultrasonography is not suitable for obese patients. It is also inaccurate for determining stone size and is regarded to have decreased sensitivity and specificity compared to CT. Radiography is still useful for the evaluation of urinary stone patients, especially when

paired with ultrasonography. KUB enables the visualisation of calcium-containing stones and assesses their radio-opaqueness and density. The sensitivity of this study is only 45–58%, mostly due to overlying bowel gas, and extra-renal or extra-ureteral calcification outbreaks. KUB is also based on the necessity of contrast administration, which may produce some adverse reactions and exposure of a patient to X-ray radiation. MRI is a non-radiation study enabling the complex evaluation of all soft tissues of the abdomen and pelvis, including the anatomical details of the kidneys and urinary tract. This examination is often suggested to pregnant women or children when radiation is contra-indicated or it is performed in patients presenting symptoms of nephropathy, who must avoid contrast administration and possible additional kidney injury. CT scans are regarded as ideal, requiring no intravenous contrast administration, and are a first-line imaging study, especially for patients with acute symptomatology of kidney stone disease, diagnosed in emergency departments. The main advantage of the study is that all stones (with small exceptions for drug-induced ones) are detectable in CT. CT reveals stone size, its location and its overall density with skin-to-stone distance, which are predictors of successful fragmentation during ESWL [19, 20].

DRUG-INDUCED URINARY STONES

The excretory system is susceptible to potential damage also caused by xenobiotics – drugs, whose adverse reactions may be present as renal or urological disorders. Adverse drug reaction (ADR) is defined as the noxious and unintended response to a drug, which occurs at doses usually administered for prophylactic, diagnostic or therapeutic purposes, or to evoke the desired modification of the physiological functions. Examples of the most common ADR developing in the kidneys and urinary tract are: intratubular crystallisation or formation of urinary stones, urinary tract infections (including cystitis), erectile dysfunction in men, urinary retention and incontinence. The possible, most dramatic consequence of ARD may be the development of acute kidney injury (AKI). Overall estimates indicate that about 14–26% of all adults and 16% of pediatric AKI cases are drug-induced. Some cases of chronic kidney disease also result from chronic drug-induced nephrotoxicity [21, 22].

In general, crystal nephropathy takes on a wide spectrum of kidney damage caused by precipitated crystals, consisting of endogenous mineral salts, end waste metabolites, proteins and/or exogenous nutrients or xenobiotics, including drugs. Crystal-induced kidney damage caused by crystals, depending on the location of the crystallisation centres and the dynamics of this process, may be divided into three basic types. In the first type, the crystals are deposited in the vascular wall, with subsequent vascular calcification, which results in renal ischemia. Type 2 crystal-induced kidney damage involves extra- and intra-tubular crystal deposition that initiates tubular cell injury, kidney interstitial inflammation development and possible tubular lumen obstruction. In the third type of the proposed classification of crystal-induced kidney injuries, a stone formation in the kidney and urinary tract, with possible obstructive nephropathy, occurs. Therefore, it can be concluded that drug-induced kidney stone disease is a special ADR, which can be categorised as a sub-type of crystal nephropathy [23].

Drug-induced stones are a rare type of stones, similarly to melamine ones or those associated with rare congenital metabolic defects, such as xanthine oxidase deficiency or alkaptonuria [24]. The urinary stones account for about 2% of renal calculi cases, although the incidence of these types of stones seems to be underestimated. First, most drug-containing stones are radiolucent in radiography (although these stones are detectable in an ultrasound study). This is the reason behind the diagnostic difficulties of this type of stones. Secondly, careful anamnesis is necessary, since the patient's detailed medical history together with establishing a detailed list of medications and dietary supplements are the basis for revealing the potential relationship between urinary stone formation and pharmacotherapy. The demonstration of the pathophysiological relationship between the drugs taken by a patient and the development of urinary stones is difficult, taking into account the possibility of recognising this clinical entity, even many years after the cessation of the given, "suspected" treatment. Moreover, the diagnosis of drug-induced kidney stone disease must take into account the problematic fact that the patient can be treated with several potentially lithogenic drugs, which makes it difficult to identify a specific one as the main aetiological factor of urolithiasis. This is very important in the context of the prevention of the development of drug-induced kidney stone disease; only precise determination of the drug that is most likely to cause urinary stone formation and its withdrawal reduces the risk of the development of the disorder. Conversely, there are also strong indications when a patient may be suspected of suffering from drug-induced urinary stones. The disease can be initially diagnosed in a patient without a history of urolithiasis, who is treated with a drug with high lithogenic potential, and when the conditions mentioned below have been fulfilled [25].

The risk factors for drug-induced urinary calculi involve both patient- and drug-specific issues. Among the factors associated with the patient, the following points should be mentioned: personal and family history of nephrolithiasis, low 24-hour urine output, aberrant low or high urinary pH, recurrent urinary tract infection episodes, malformation predisposing to urinary stasis and stone formation (e.g. pre-existing calculi, prostatic hypertrophy), metabolic disorders associated with biochemical lithogenic abnormalities (e.g. hypercalcuria), environmental factors (e.g. hot temperatures causing excessive sweating). One can also distinguish several attributes of the drug itself, predisposing to the development of urinary stones: the administration of high doses of the compound, long-term treatment, low aqueous solubility of high urinary excretion of the drug and/or

its metabolites and polytherapy, as well as co-administration of other drugs that may cause pharmacokinetic interactions, interfering with the excretion of lithogenic substances and xenobiotics [25].

Two main types of drug-induced urinary stones can be distinguished, taking into account the main pathomechanism of their formation. The first group includes stones composed principally of the drug and/or its metabolites. These stones are mostly formed by poorly soluble compounds, for which the kidneys are the main route of elimination. Therefore, in accordance with the general, aforementioned pathophysiological premises, when the solubility equilibrium is exceeded, these drugs may undergo nucleation and crystallisation (both homogeneous and heterogeneous) in supersaturated urine. The second group of drug-induced urinary stones are those classified as a sub-type of "metabolic stones", due to the evoked metabolic effects of a drug, primarily on calcium or purine metabolism [25, 26]. Many drugs may induce urinary stone development by affecting the pH of urine (in such a way that the solubility of many endogenous substances decreases), alternation of the glomerular filtration and tubular secretion/reabsorption of the endogenous substances, or impairing the balance and action of crystallisation promoters/inhibitors (while enhancing the effects of the promoters of the phenomenon) [27]. To sum up, the physiological and biochemical disturbances, which form the basis for urinary stone development (nucleation, crystal growth, crystal aggregation) may be also drug-evoked. Since the chemical composition of drug-induced metabolic stones does not contain the drug itself, but appears identical to the non-drug dependent counterparts, the differential diagnosis of those drugs is particularly difficult and requires careful assessment [25–28].

The characteristics of both types of drug-induced urinary stones are given in Table III.

CONCLUSIONS

Kidney stone disease is an important disorder that can periodically manifest itself with painful ailments, and in the long-term may even lead to serious complications. The disease can also develop as adverse nephrological and urological drug reactions. Drugs that are considered to have high lithogenicity potential may cause metabolic abnormalities predisposing to the crystallisation and precipitation of the physiological components of urine or they may crystallise themselves in the urine. Therefore, treatment based on the use of drugs perceived as highly lithogenic, especially in patients with other risk factors for the development of urinary stones, must be carefully monitored for the safety of the implemented pharmacotherapy. Due to the fact that drugs that may cause the formation of urinary stones belong to different pharmacological groups, the possibility of drug-induced kidney stones should be taken into account by practitioners of various specialties in planning pharmacotherapies and assessing their risk.

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ORCID and contributionship
Łukasz Dobrek - 0000-0001-5049-0026 [A-F]

Conflict of interest
Author declare no conflict of interest.

CORRESPONDING AUTHOR
Łukasz Dobrek
Department of Clinical Pharmacology,
Wroclaw Medical University,
ul. Borowska 211A, 50-556, Wroclaw, Poland;
e-mail: xlukaszx@onet.eu

Received: 15.06.2020
Accepted: 31.08.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

MEDICAL REHABILITATION SYSTEM AND ITS QUALITY CONTROL IN DEVELOPED COUNTRIES OF THE WORLD

DOI: 10.36740/WLek202009227

Viktor I. Shevchuk, Oksana B. Yavorovenko, Natalia M. Belyaeva, Iryna V. Kurylenko
RESEARCH INSTITUTE OF REHABILITATION (MEDICAL SCIENTIFIC TRAINING CENTER) OF VINNYTSIA NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: To review scientific literature dealing with evaluation of medical rehabilitation effectiveness and quality in the world.

Materials and methods: Review and generalization of scientific literature on the criteria of evaluation of medical rehabilitation quality in advanced industrialized societies.

Conclusions: Despite differences in the structure of medical rehabilitation in world societies, the end point is similar – assessment of quality of life of a sick person, measured by various criteria and standards. This experience is of great value for the development of national system of rehabilitation services.

KEY WORDS: medical rehabilitation, assessment of quality, patients

Wiad Lek. 2020;73(9 p. II):2051-2056

INTRODUCTION

In market economy conditions, one of the most important tasks of public health and social protection authorities is to ensure a sufficient quality of life for socially disadvantaged groups of population [1]. Adequate functional status of disabled, elderly, and sick individuals can be achieved by comprehensive rehabilitation therapy, consisting of medical, social, and professional aspects. The most important component of rehabilitation care, determining the effectiveness of rehabilitation in general, is medical rehabilitation [2]. Therapeutic measures carried out within the program of medical rehabilitation of disabled and sick individuals are part of the system of medical and preventive care, which can be controlled using rich experience of national healthcare system [3-7]. Unfortunately, public health authorities do not focus on the assessment and quality control of medical rehabilitation in disabled and sick persons. The lack of technological and medico-economic standards for assessing the quality of rehabilitation care for sick and disabled individuals makes it impossible to use unified approaches to rehabilitation therapy in medical institutions of different forms of property, as well as hierarchical relationship between its stages.

THE AIM

To present the review of scientific literature dealing with evaluation of medical rehabilitation effectiveness and quality in the world.

MATERIALS AND METHODS

Review and generalization of scientific literature on the criteria of medical rehabilitation quality assessment in advanced industrialized societies.

REVIEW AND DISCUSSION

In recent decades, many countries around the world have been developing the system of medical rehabilitation aimed at restoration of functional ability and quality of life to those with physical impairments, as well as their maximal integration or reintegration in society and prevention of disability [8-12]. It should be noted that each country arranges the system of medical rehabilitation according to its national requirements.

For example, in Germany rehabilitation therapy is carried out at the in-patient and outpatient medical institutions and the so-called day-care clinics [12, 13]. In-patient institutions include rehabilitation centers, rehabilitation departments at large hospitals, sanatoria and resort centers. But outpatient treatment is preferred if possible. Such forms of rehabilitation services as day-care facilities and hospitals for patients with chronic diseases and disabled individuals who do not require continuous all-day medical supervision are also common. To determine the rehabilitation efficiency, the method of questioning patients at discharge from the rehabilitation center is used [14]. Currently, rehabilitation standards are being developed to analyze and guarantee the quality of therapy course. Public health service is based on well-structured health insurance system consisting of compulsory state insurance (CSI) and private health insurance funds.

In France, much of inpatient rehabilitation measures are carried out as concomitant restorative therapy during the patient's stay in the hospital. In-patient treatment is commonly divided into categories depending on duration of treatment: *curteduree*, or short-term treatment for acute condition; *moyenneduree*, or medium duration treatment, implying rehabilitation or health-improving therapy; *longueduree*, or long-term treatment in centers for disabled [15]. Sometimes rehabilitation

in France is determined as *"moyensejour"*, or treatment of medium duration. In French rehabilitation centers, the quality management process has not been elaborated in details due to structural peculiarities of clinics. A rehabilitation center can receive the permission to treat patients if it fulfills certain standard requirements, e.g. training room equipment, the presence of at least one swimming pool, balneotherapy and physiotherapy rooms, including a place for loop tables, electrotherapy apparatuses, rooms for ergotherapy, gypsum rooms, rooms for training devices, rooms for language training, halls and classes for school, professional and social reintegration, leisure facilities [12].

Currently, public consultations are in progress as to medical rehabilitation significance, having focused on funding shortage of rehabilitation centers and clinics [16]. Financing of private clinics, being fixed by the district prefect, is insufficient as well. But low funding for rehabilitation services is associated with decreased therapeutic potential, and treatment itself is limited to nursing process and is not aimed at reintegration of patients.

Cost-effectiveness of many clinics is not guaranteed, since health insurance providers financing rehabilitation programs, contemplate to minimize co-payment, making medical rehabilitation practically inaccessible because of initially high cost of treatment. Public consultations on the development of rehabilitation service system in France address the problems of giving longitudinal attention to disabled individuals, as health insurance system does not provide proper care for such patients, as in Germany. Because of insufficient number of affordable skilled nursing facilities, rehabilitation departments are overcrowded with disabled patients, and therefore cannot be used as intended. The only financing structure for medical rehabilitation service in France is medical care insurance. It is a part of general social insurance system and covers about 80% of population [17].

In Switzerland, hospitals have a multidisciplinary principle of treatment being staffed with appropriate specialists [18]. Rehabilitation treatment plan of each hospitalized patient is extended and subdivided into weekly plans, the goals of rehabilitation are determined. Doctors are responsible for further diagnostics, administrations, coordination and control of therapeutic measures in accordance with rehabilitation plan, institution of special forms of treatment, keeping clinical recording, making further recommendations for rehabilitation after discharge of the patient and writing hospital discharge list with epicrisis, which is sent to the family doctor and financing organization. Hospital discharge epicrisis has no a unified structure; instructions concerning working capacity of patients are given as needed. In Swiss medical rehabilitation system, the concept of quality management is incorporated into the Health Insurance Act. Certain criteria, associated with staffing level, are crucial in determining the potential capabilities of rehabilitation clinic to perform rehabilitation therapy. For example, the number of physical therapists should provide at least 2.5 hour sessions per patient per day, otherwise quality of treatment is considered to be poor. Besides, the level of professional competence confirmed by relevant certificates, is checked. The following minimal staff should be provided at 90% load of beds: 0.05 doctors, 0.2 nurses, 0.2 physical therapists per bed. Nongovernmental organization "Agency in Promotion of Evaluation and Quality" (APEQ) establishes a set of quality criteria and monitors rehabilitation clinics in accordance with ISO 9001 standards [19]. According to those criteria and standards, health care providers can obtain internationally acceptable certificates for quality management systems. Medical rehabilitation services are funded by state insurance institutions.

In Spain, rehabilitation therapy system at in patient specialized rehabilitation clinics is generally underdeveloped, as evidenced by the level of availability of rehabilitation facilities – about 0.05 rehabilitation beds per 1000 population [12]. There are only 24 rehabilitation centers for 1952 beds in the country. Most of rehabilitation centers are private. In general, inpatient health care coverage is lower than in other European countries. Sanatorium and resort care in Spain does not belong to generally accessible sector of national public health system being excluded from the list of paid health care services. Public health care system is financed by tax-payers. Medical rehabilitation in Spain is a part of primary outpatient care financed by tax-payers and is carried out on an outpatient basis in primary care centers [20]. There are about 2500 such centers where every citizen can get diagnostic, therapeutic, preventive and rehabilitation services.

In the United Kingdom, medical rehabilitation as well as rehabilitation in general is placed between two separate systems: National Health Service (NHS) on the one hand, and Social Security System on the other [21]. Such intermediate position creates some difficulties for assuring medical, professional and social rehabilitation services. The problem is delineation of responsibilities between National Health Service and Social Security System. In the UK, medical rehabilitation therapy is usually carried out as part of inpatient treatment. The outpatient care is provided by qualified district and community nurses responsible for home health service of patients in need. Rules and regulations concerning quality management control are rarely included in the budget agreement between municipal health care districts and hospitals and are commonly solved internally. The control of medical activity is regulated in personnel of the hospital by means of command-and-control structure headed by director general. The so-called clinical audit is commonly used. When purchasing medical services for their patients, family doctors are responsible for quality of outpatient and inpatient therapy. The financing is provided by state budget at taxpayers' expense.

In Sweden, the tasks of rehabilitation medicine are professional reintegration, vocational education, employment assistance, arranging adequate living conditions after discharge from the hospital, in addition to further diagnosis and in patient treatment, establishing a connection with social services, agencies for labor and health insurance providers if necessary [22]. Physical and rehabilitation medicine experts are responsible for physiotherapy and ergotherapy procedures, provide advice to those referred by family doctors or agencies for labor. Having deep knowledge of psychology, logopedics and social medicine, they are guided by principles of urgency medicine measures. Primary health care is usually provided in medical centers of provinces consisting of hospitals and

outpatient clinics [23]. According to the guidelines of the Ministry of Health and Social Affairs, each patient has the right for individual rehabilitation plan [24]. Assurance of quality in rehabilitation departments is controlled by the Swedish Society of Rehabilitation Medicine, which issues quality certificates. In accordance with Regulations on quality management in health care, all funding public health bodies are obliged to participate regularly in quality control monitoring. Each hospital is obliged to develop its own quality control system. Quality control registers have been made for self-monitoring of health care vendors as well as governmental quality control. Currently, chronic pathology is one of the major problems under discussion in the country. About 45% of individuals with chronic diseases are disabled for more than twelve months. Early disability retirement is unprofitable for retirement insurance system because of redistribution of financial expenditures but not problem solution. Medical rehabilitation is of great importance for public health in Sweden implying prevention of early disability in many cases. In Sweden, public health is 95% state-funded.

In the USA, rehabilitation centers are part of scientific and medical associations [25]. They are 30 multidisciplinary medical centers outfitted with state-of-the-art equipment. Inpatient rehabilitation therapy consists primarily of early rehabilitation carried out in rehabilitation departments of large hospitals [23]. Outpatient medical service is nursing care providing home rehabilitation services. To make a contract with the so-called Health Maintenance Organizations (HMOs), healthcare centers are to report on quality and effectiveness of their work. Functional Independence Measure (FIM) has become widely used, serving as a tool for statistical comparison of rehabilitation outcomes between rehabilitation institutions [26]. Hospitals in the United States are subjected to strict quality control and are obliged to verify accreditation every 3 years in order to prolong the right for providing medical services to people. In this way the state control and impact on the health care system are exercised.

Most of above mentioned peculiarities in the US health care and rehabilitation system are rather specific and cannot be transferred to other countries. At the same time, certain economic aspects are taken as a model in other countries including Europe. Thus, a prospective payment system on the basis of diagnosis related groups (DRG) was introduced in 2004 in Germany [27]. Similar to many other countries where DRGs are in use such as the USA and Australia, one of the major goals for implementation of this hospital reimbursement system has been reducing health care expenditures and cost control by setting hospitalization payment for all payers at a fixed DRG-rate per admission. Hospitals have an interest in rapid transfer of patients to early rehabilitation, eventually leading to positive impact on both rehabilitation and treatment outcomes. In the USA there is a need in arrangement of early rehabilitation departments as well as further development of practical rehabilitology as a whole. The US system of inpatient treatment financing on the whole, and rehabilitation treatment (inpatient or outpatient) in particular, is multidimensional being represented by a large number of public or private insurance options.

In Finland, the Ministry of Social Affairs and Health is the body responsible for implementation of laws in the field of rehabilitation for disabled individuals. The coordination of actions between various sectors of health care system in this field is performed by National Coordination Committee on Rehabilitation, National Rehabilitation Council, municipal councils and cooperation groups in provinces. Medical rehabilitation can be provided either in a rehabilitation center or as outpatient therapy allowing the patient to live at home [28]. In addition, rehabilitation at sole discretion and psychotherapy rehabilitation are available. In Finland, continuity in therapy stages is practiced, thereby improving the quality of rehabilitation and shortening its time [29]. According to the National Pensions Act, medical rehabilitation in Finland is financed by the Social Insurance Institution of Finland. Insured individuals receive rehabilitation therapy in accordance with the Rehabilitation Services Act [30].

CONCLUSIONS

Despite considerable differences in organization of medical rehabilitation in industrialized countries, methodological approaches are similar in terms of basic purposes and methodical principles of rehabilitation medicine.

It is the assessment of quality of life of disabled individuals that determines the effectiveness of rehabilitation therapy in many countries of the world. Rehabilitation success is measured by instruments that assess performance of activities of daily living. To assess final functional status of patients after rehabilitation therapy, and thus its effectiveness, objective and subjective factors are considered: questionnaires, equipment of rehabilitation departments, adequacy of the staff, competence level of hospital staff, interdepartmental control, quality control registers. Functional independence measure (FIM) is a widely accepted functional assessment measure used during inpatient rehabilitation in many countries. Besides, administration of stage-to-stage treatment leads to minimization of negative effects and improvement of rehabilitation quality.

International experience in functioning of medical rehabilitation systems in industrialized countries as well as means of their quality assessment, presented in the review, can serve a valuable example for Ukrainian health care experts in the development of effective national system of rehabilitation medicine.

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ORCID and contributionship:

Viktor I.Shevchuk: 0000-0003-1105-4795 [A, D, F]
Oksana B. Yavorovenko: 0000-0001-9196-5841 [D, E]
Natalia M. Belyaeva: 0000-0002-0500-8082 [B, D]
Iryna V. Kurylenko: 0000-0001-5492-4573 [B, F]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Oksana B. Yavorovenko
Research Institute Of Rehabilitation
(Medical Scientific Training Center)
Of Vinnytsia National Pirogov
Memorial Medical University
104 Khmelnytskyi Highway, 21029 Vinnytsia, Ukraine
tel.: + 380938003890, +380984677614
e-mail: reab@ukr.net; oksanayavorovenko@gmail.com

Received: 21.10.2019
Accepted: 30.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

ENSURING THE RIGHT TO HEALTH OF STAFF OF THE UNITED NATIONS

DOI: 10.36740/WLek202009228

Tetiana L. Syroid, Lina O. Fomina, Oleksandr A. Havrylenko
V.N. KARAZIN KHARKIV NATIONAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: of the study is to characterize the internal acts of the United Nations on the regulation of the right to health of its staff.

Materials and methods: Achieving the purpose of the study is ensured due to the analysis of internal acts of the United Nations, doctrinal sources on the issue selected. The methodological basis is a number of special and general methods.

Conclusions: The right to health guaranteed by the International Bill of Human Rights is comprehensive and closely linked to labour human rights. International civil servants of the UN system are not exempt. Thus, within the United Nations, a number of acts have been developed, the provisions of which set out recommendations aimed at reducing possible cases of infection of workers, maintaining their mental health while on quarantine, informing staff about their actions in case of illness, testing workers, etc. However, these acts need to be improved.

KEY WORDS: COVID-19, physical state, personnel, international intergovernmental organizations

Wiad Lek. 2020;73(9 p. II):2055-2061

INTRODUCTION

The human right to health is guaranteed in a number of international human rights treaties and in national law of most states. The Declaration of Alma-Ata, adopted by the International Conference on Primary Health Care in 1978, states that health, as a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is a fundamental human right; and achieving the highest level of health is the world's most important social task, which requires the joint efforts of many social and economic spheres of society. It is worth noting that the observance of the right to health is closely linked to other human rights, particularly, in labour activity, as the effective performance of official duties is possible only if safe working conditions are ensured. This issue becomes significantly relevant during the rapid spread of coronavirus infection COVID-19. In this regard, it is important to pay attention to the issue of observance of the right to health of staff of international intergovernmental organizations, including the United Nations (hereinafter – the UN, the Organization), whose representatives ensure the goals and objectives proclaimed in the UN Charter by holding joint meetings, business trips, reception of persons sent by member states, work with victims of human rights violations, etc. Such activities are potentially threatening the lives and health of such workers in a pandemic. Given this, the topic of the research chosen is relevant.

The issue of international legal regulation of the right to health has been the subject of research in the works of a number of Ukrainian and foreign scientists, including: Alicia Ely Yamin, Raymond Agius, Steven D. Jamar, Eglė Venckienė, A. Abashydze, T. Anakina, M. Baimuratov, M. Buromenskyi, O. Kyivets, N. Khendel and others. Some studies of the legal status of international civil servants were conducted in the works of Gerhard Ullrich, Dag Hammarskjöld, Mona Ali Khalil, Ye. Vasco, P. Fomin, O. Shulipa, and others. However, this topic requires further detailed research.

THE AIM

The aim of this article is to describe the provisions of the United Nations internal instruments governing the right to health of international civil servants.

MATERIALS AND METHODS

The study is based on the analysis of international human rights agreements at the universal and regional levels, the provisions of the UN internal acts on ensuring the right to health of its staff, scientific achievements in this area. The methodological basis is a number of special and general methods, in particular, the dialectical method, axiological, formal, and so on. The use of the axiological method allowed us to understand the importance of the right to health of the UN staff in the context of spread of coronavirus infection and its enshrinement in internal acts of the Organization. The formal and legal method used to analyse the provisions on the right to health of the UN staff, including the classification and systematization of mea-

sures related to the exercise of this right. The application of a set of scientific methods together with the principles, as well as modern scientific approaches made it possible to achieve the purpose of the study.

REVIEW AND DISCUSSION

The right to health is one of the fundamental human rights and freedoms guaranteed by international law at the universal and regional levels. Thus, the Universal Declaration of Human Rights of 1948 proclaimed the right of everyone to life (Article 3) and the standard of living, including food, clothing, housing and medical care and necessary social services, necessary for the maintenance of health and well-being of themselves and their family, and the right to security in case of unemployment, illness, disability, widowhood, old age or other lack of livelihood in circumstances beyond their control (Article 25) [1]. The member states of the International Covenant on Economic, Social and Cultural Rights of 1966 recognize the right of everyone to the highest attainable standard of physical and mental health (Part 1, Article 12) [2]. The Charter of Fundamental Rights of the European Union of 2000 enshrines a rule according to which everyone has the right to preventive treatment and medical care (Article 35) [3]. This right is also enshrined in a number of special international agreements on human rights (Convention on the Rights of the Child of 1989) (Article 24), the UN Convention on the Elimination of All Forms of Discrimination against Women of 1979 (Article 11), and Convention on the Rights of Persons with Disabilities of 2006 (Article 25), etc.).

It should be also emphasized that the right to health is closely linked to and depends on the realization of other human rights guaranteed by the International Bill of Human Rights, including the right to food, housing, employment, education, human dignity, life, etc.

The UN Committee on Economic, Social and Cultural Rights has stated that these and other rights and freedoms are linked to the elements of the right to health. According to the Committee's interpretation, the right to health includes not only the right to prompt and adequate health services, but also to such fundamental preconditions of health as, especially, safe working conditions… (para. 11) [4]. This thesis is supported by the General Comment of the UN Committee on Economic, Social and Cultural Rights № 23 (2016) on the right to fair and favourable working conditions, according to which the fundamental aspect of the right to fair and favourable working conditions is closely linked with other rights, especially with the right to the highest attainable standard of physical and mental health, is the prevention of accidents at work and occupational diseases (para. 25) [5].

Thus, the International Covenant on Economic, Social and Cultural Rights of 1966 stipulates that measures to be taken by State parties to the Covenant for the full realization of the right to health include, inter alia, the improvement of all aspects of environmental and occupational health in industry (para. b, section 2 of Article 12) [2]. The Charter of Fundamental Rights of the European Union of 2000 also guarantees every employee the right to work in conditions that ensure the protection of his health… (Article 31) [3]. The right to safe and healthy working conditions is also regulated by the European Social Charter (revised) of 1996, the parties to which have undertaken to develop, implement and review regularly the consistent national policies in the field of labour protection, health and safety protection in the workplace, the main purpose of which is to improve labour protection and occupational hygiene, as well as prevention of accidents and injuries resulting from occupational activities…; adopt rules on occupational safety and health; ensure compliance with such rules through measures to monitor compliance with their requirements; to promote the gradual development of occupational hygiene services intended for all employees, the main task of which is to carry out preventive and advisory functions (Article 3) [6].

The UN Committee on Economic, Social and Cultural Rights also noted that the measures provided for in the Covenant of 1966 to improve all aspects of environmental and occupational health in a workplace include, inter alia, measures to prevent accidents at work and occupational diseases; the need to ensure an adequate supply of safe drinking water and basic sanitation services; prevention and reduction of the impact on people of harmful substances, such as radiation and hazardous chemicals, or other harmful environmental conditions that directly or indirectly affect human health. In addition, from a reasonable point of view, occupational health allows to eliminate as much as possible the causes of harmful factors of the working environment [4].

The abovementioned has been confirmed in scientific researches. Thus, Steven D. Jamar notes that the scope of the right to health is much broad and affects many interrelated areas. He notes that Art. 12 of the Covenant on Economic, Social and Cultural Rights obliges States to act to protect and promote health by taking measures in the field of antenatal, neonatal and child health care, "all aspects of environmental and occupational hygiene", disease prevention, treatment and control, and the provision of health services to all become ill… The WHO Global Strategy for "Health for All up to 2000" formulates an approach to primary health care that includes all aspects of nutrition, sanitation, and the environment, occupational safety, health care, education and training of medical staff, and health initiatives. In view of the above, the author concluded that these numerous areas of activity provide a reliable and complete, though not exhaustive, list of areas in which the state must act to fulfil its obligation to ensure the human right to health [7].

Eglė Venckienė also drew attention to the fact that the right to health care is one of the fundamental rights without which a person will not be able to enjoy other rights: economic, political and social rights. It includes the right to better physical and mental health. The author notes that the analysis of the provisions of international legal acts show that the right to health care enshrined in

international treaties and declarations has evolved from a fundamental human value into an independent right, the implementation of which includes an increasing number of measures [8].

Alicia Ely Yamin noted in her work that the right to health includes both health care and health conditions… as well as the right to participate in decisions that affect health… [9].

That is, the right to health is closely interrelated with other rights, including labour rights. International civil servants, who ensure the continuous and efficient functioning of international intergovernmental organizations, including the United Nations, are not an exception, said Dag Hammarskjöld at his lecture at Oxford University.

Thus, the UN has adopted a number of acts that enshrine the rights and responsibilities of its employees, the peculiarities of international civil service, the procedure for protecting their labour rights, as well as regulating issues related to the right to health. The UN Staff Rules and Regulations define the authority of the UN Secretary-General to establish a staff social security plan that includes health regulations. In addition, staff may be invited to participate in the UN Health Insurance Plan on terms to be determined by the Secretary-General (Rule 6.6) [10].

In order to prevent illnesses among employees, which may pose a threat to the health or safety of others, they may from time to time be offered a medical examination by the Director of the United Nations Medical Service or a physician appointed by the Director of the UN Medical Service. Staff members may also be asked to undergo such medical examinations and vaccinations as may be necessary, in the opinion of the Director of the UN Medical Service or a physician appointed by the Director of the UN Medical Service, before or after their return from mission (Rule 4.19). In addition, employees may be asked at any time to submit a medical certificate of their health or to undergo a medical examination at the UN Medical Service or from a medical practitioner designated by the Director of the UN Medical Service. If, in the opinion of the Director of the UN Medical Service, a staff member's health is adversely affected by his or her ability to perform his or her functions, the staff member may be ordered not to go to work and asked to seek the assistance of a qualified practitioner. The employee must comply with any instructions or suggestions in a timely manner. In addition, the employee is obliged to notify immediately the UN doctor of all cases of infectious diseases in their family and of any quarantine affecting their family. In such a case or in the event of any other circumstances that may affect the health of others, the Director of the UN Medical Service decides on possible dismissal of the employee. In this case, the employee receives in full the salary and other benefits due to them during the period of permitted absence from work (Rule 6.2 (f) (g)) [10].

It is worth noting that the issue related to the implementation and protection of the right to health has become significantly relevant in the context of the spread of coronavirus infection COVID-19. In his speech, the UN Secretary-General said that as the world struggled with COVID-19, the UN was strengthening its readiness and ability to combat the spread of coronavirus among its workforce so that the Organization could continue to fulfil its vital mandate worldwide. He noted that as of March 2020, the UN has 763 health workers working in a variety of health facilities around the world, including at headquarters and field offices that provide UN support services in their vital work [11].

In order to prevent morbidity among staff, the Organization has adopted a number of acts on disease prevention, pandemic procedures (administrative guidelines, Guidelines for emergency support plans, Guidelines for crisis preparedness for staff and families, Alternative working conditions in the context of COVID-19, Guide to the use of masks by UN staff in the context of COVID-19, etc.).

For instance, during the COVID-19 outbreak and its high threat to public health, UN staff was divided into two categories: staff performing critical tasks and staff performing non-critical tasks. Critical staff includes staff assigned critical functions in the event of office closures due to the COVID-19 outbreak to ensure business continuity; non-critical staff – employees who will not be required to work during the closure of the office. When selecting employees as critical staff, the heads of structural units must ensure the following: physical protection of staff and facilities; medical care for staff; maintenance of telecommunication and information technologies; ability to communicate with other organizations and governments; maintenance of engineering networks (electricity, water supply and sewerage), etc. The number of critical staff should be kept to a minimum and include heads of offices, local security management teams, medical staff, security staff, human resources (including consultants), finance, information and communication, and so on. Employees assigned as critical staff should be informed of the consequences of such assignments and that they may be required to remain in quarantine for 14 days in order to limit any possible adverse effects on their part. In order to ensure the continuity of operations, UN offices can be virtually opened during physical closure [12].

In particular, from 16 March 2020 all employees in New York are required to work distant and exercise their duties remotely, unless their physical presence in the building is required to perform basic work in New York and around the world [13].

In addition, in view of the rapid development of the epidemiological situation and the uncertainty regarding the dynamics of COVID-19 transmission, a Meeting Guide was prepared within the UN, in particular, it was recommended to take into account the risk assessment considerations set out in the "Civil Health Protection for mass events: basic considerations" [14].

However, in the event of any meetings, staff members are encouraged to use personal protective equipment to be provided by the Organization based on workplace risk assessments and the UN Directors' Healthcare Risk Reduction Plan through COVID-19. The Staff is also

encouraged to take all measures deemed reasonable in their places of residence, such as work at home, physical distance, hand hygiene and the use of personal protective equipment, etc. [15].

The Secretary-General and the heads of various units in a number of duty stations around the world have also decided to restrict physical access to UN territory in order to curb the spread of COVID-19, while work continues in virtual mode. In all units in the field of service where such a decision has been made, employees must continue to work distant, except when their physical presence is necessary to perform critical functions. In practice, this means that employees have to perform their duties on a distant basis from an alternative place of work, usually from home. This measure was taken in response to the emergency situation caused by the spread of COVID-19, and is designed to help ensure the sustainability of the Organization at a time when it is extremely important to minimize social contacts. However, at the end of each working week, staff members should mark distant working days in the Umoja system, and when entering information into Umoja, employees should select a new Telecommuting-COVID-19 item from the proposed list [16].

In addition to the tools listed above, the United Nations Office uses a "3-phase system for activating appropriate actions" to manage and coordinate emergency actions in the field of health in the UN system, including COVID-19. This system can be activated in response to disease outbreaks and other health emergencies. Three stages include: stage 1 "Standby"; stage 2 "Active risk mode"; Stage 3 "Emergency mode". During the first phase, all duty stations must be prepared for the fact that such an outbreak may affect their daily activities. Therefore, it is necessary to prepare, review and update constantly health response plans and strategies and to deploy preparedness actions, including information, education on specific diseases and targeted communication. In the mode of active risk mode, which is realized when the outbreak reaches the place of work with some prevalence in the community, it is necessary to implement active measures to reduce risk in the workplace. Measures include the organization of meetings and staff reductions, with a special focus on vulnerable employees, such as employees with weakened immune systems or concurrent illness. The workplace remains open, but risk mitigation measures are being taken, including social distancing and other activities. In the third mode, full implementation of risk management and medical response measures is required due to the large number of cases reported in the host country [17].

If a UN staff member had contact with a person with acute respiratory symptoms such as fever, cough or shortness of breath in the course of their day-to-day work, they should take a number of steps to minimize the risk of infection, whether COVID-19 or any other respiratory disease. These steps may vary for each workplace based on guidelines from UN health services and local health authorities, and UN staff should be familiar with the written protocol of the workplace / office. Thus, an employee who has symptoms of acute respiratory disease (cough, shortness of breath), while at work, must: distance himself from other people at a distance of at least 1 metre (or be in a separate room); cover the nose and mouth with a cloth when coughing or sneezing and wear a surgical mask; return home immediately and stay at home until the respiratory symptoms disappear; consult a physician first by telephone to report symptoms and any travel or possible effects. The healthcare professional will advise staff on any necessary testing or treatment. In addition, information on COVID-19 should be publicly available, including all measures taken in the workplace to ensure safety and health of each employee [18].

The UN also offers COVID-19 testing services to UN staff and staff working in UN permanent and supervisory missions in New York who feel unwell and meet clinical testing criteria. In this situation, the employee should send a letter to osh@un.org to request testing and indicate the employee's name, date of birth, index (if UN), organization (e.g. UNICEF, UNS, Permanent Mission, etc.), full address with postal code, contact phone. Testing is not available to dependents [19].

It is worth noting that the restriction of social activity, the duration of duties using information and communication technologies, while at home, other radical changes in lifestyle through the introduction of quarantine measures can affect the psychological health of individuals. With this in mind, the UN Guidelines for the Protection of Mental Health during COVID-19 set out a number of recommendations aimed at maintaining their well-being during this period. Among them: provision of basic needs (sufficient rest time, observance of a balanced diet, physical activity, etc.); minimization of factors that affect mental health negatively (reduction of smoking, alcohol consumption, obtaining reliable information about the situation with COVID-19 in verified sources to prevent misinformation); keeping in touch (communicating with friends, colleagues to reduce feelings of loneliness); defining clear boundaries between personal life and work (compliance with the work regime, taking a break), etc. [20].

Raymond Agius in his paper on COVID-19 and occupational health, also emphasizes that traditional occupational health measures, such as segregation, ventilation, personal protective equipment, etc., must be comprehensive to prevent the virus from recurring. Employees returning to work should be screened for symptoms and contact history.

CONCLUSIONS

Thus, based on the abovementioned, it can be concluded that the right to health guaranteed by the International Charter of Human Rights is comprehensive and closely linked to labour human rights, in particular the creation of safe working conditions, prevention of occupational diseases and injuries. International civil servants of the UN system are not exempt, as they ensure the continuous functioning of the Organization and the achievement of its goals and the ideals it aspires. UN staff exercise a wide

range of responsibilities around the world, accompanied by a significant number of contacts with other colleagues, government officials, and so on. This situation has become threatening in light of the active spread of COVID-19. Thus, the UN has adopted a set of internal acts that regulates the legal status of employees in detail, including issues related to their health. However, in view of the expansion of the pandemic, the Organization has developed a number of acts, the provisions of which set out recommendations aimed at reducing possible cases of infection of workers, maintaining their mental health while on quarantine, informing staff about their actions in case of symptoms of acute respiratory diseases and regulates the issue of the continuous functioning of the UN during this period. In addition, the UN has created conditions for testing workers for COVID-19, provided that they meet clinical criteria, however, such testing is not available to members of their families, that may significantly increase the incidence among staff.

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ORCID and contributionship:

Tetiana L. Syroid: 0000-0002-8165-4078 [A, B, D, F]
Lina O. Fomina: 0000-0002-8756-4006 [A, B, D, F]
Oleksandr A. Havrylenko: 0000-0001-5554-4919 [A, E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Tetiana L. Syroid
V. N. Karazin Kharkiv National University
4 Svobody Sq., 61022 Kharkiv, Ukraine
tel: +380677042283
e-mail: syroid02@gmail.com

Received: 04.06.2020
Accepted: 10.08.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

MODERN ENDOVASCULAR TREATMENT METHODS FOR ERECTILE DYSFUNCTION: A CRITICAL ANALYSIS

DOI: 10.36740/WLek202009229

Magdalena Piegza[1], Mateusz Paterak[2], Michał Błachut[1], Jacek Piegza[3]

[1]CHAIR AND DEPARTMENT OF PSYCHIATRY IN TARNOWSKIE GORY, SCHOOL OF MEDICINE WITH THE DIVISION OF DENTISTRY IN ZABRZE, POLAND, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, ZABRZE, POLAND

[2]STUDENT SCIENTIFIC SOCIETY AT CHAIR AND DEPARTMENT OF PSYCHIATRY IN TARNOWSKIE GORY, SCHOOL OF MEDICINE WITH THE DIVISION OF DENTISTRY IN ZABRZE, POLAND, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, ZABRZE, POLAND

[3]3RD CHAIR AND DEPARTMENT OF CARDIOLOGY, SCHOOL OF MEDICINE WITH THE DIVISION OF DENTISTRY IN ZABRZE, SILESIAN CENTER FOR HEART DISEASES, POLAND, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, ZABRZE, POLAND

ABSTRACT

75% of men with coronary artery disease confirmed by coronarography have erectile dysfunction in history, while 75% of patients with a vascular etiology of ED have significant stenoses in penile arterial vascularization. Patients with coronary artery disease have shown a relationship between the range of the lesions in the coronary vessels and erectile dysfunction intensity.

This paper aims at attempting to systematize the knowledge of the benefits and drawbacks of nonsurgical endovascular treatment methods for erectile dysfunction with confirmed vascular causes. It analyzes seven studies which assess the results of erectile dysfunction treatment with percutaneous angioplasty. It also mentions the limitations of the cited works and formulates relevant conclusions.

Conclusions: The analysis shows that endovascular procedures in erection-related arteries are safe in a specially selected group of men. It is necessary to conduct further studies to define an appropriate group of patients who have a chance of benefiting optimally from the endovascular treatment of erectile dysfunction in a long-term follow-up.

KEY WORDS: atherosclerosis, angioplasty, erectile dysfunction, endovascular revascularization

Wiad Lek. 2020;73(9 p. II):2060-2075

INTRODUCTION

Valid medical classifications define erectile dysfunction (ED) as the inability to achieve or maintain an erection that is sufficient for a satisfactory sexual intercourse or the presence of at least one of the following symptoms in at least three-fourths of intercourse attempts: difficulty in achieving an erection during sexual activity, difficulty in maintaining the erection till its end or a pronounced loss of penile firmness during the erection. Both diagnostic systems (ICD-10 and DSM-5) require that those symptoms persist for at least six months [1]. This dysfunction is one of the most common sexological problems. Its probability increases with age: it affects 30.7% of men aged 57–64, 44.6% of men aged 65–74 and 43.5% of men aged 75–85 [2]. ED is treated as an elevated risk marker for cardiovascular system diseases. 75% of men with coronary artery disease (CAD) confirmed by coronarography have ED in history [3].

Moreover, 75% of patients with a vascular etiology of ED have significant stenoses in penile arterial vascularization. The latter includes: the internal iliac artery, the internal pudental artery, the dorsal artery of penis and the cavernosal artery [4, 5]. Furthermore, patients with CAD have shown a relationship between the range of the lesions in the coronary vessels and the intensity of ED symptoms [6].

Many factors suggest that endothelium damage may be the common pathophysiological mechanism behind CAD and ED. Consequently, a reduction of cardiovascular risk factors owing to lifestyle change and pharmacotherapy, described in a meta-analysis of 740 patients from six clinical trials conducted in four countries, significantly increased the IIEF-5 (International Index of Erectile Function) score [7]. The International Index of Erectile Function (IIEF-5), colloquially called the erectile dysfunction questionnaire, is used to assess the presence and intensity of erectile dysfunction in the last six months and is constantly applied in clinical trials [8].

The vascular causes of erectile dysfunction often coexist with a weaker response to phosphodiesterase type 5 inhibitors (PDE5I). It is estimated to concern 50% of men with ED [9].

It has been proved that as many as 90% of patients with a weak response to PDE5I show significant atherosclerotic lesions which cause arterial insufficiency in angiography [10-12].

There was shown in some publications that arterial endovascular treatments could contribute to improvement in 63%- 65% cases [13, 14].

Table 1. The results of the described research studies.

Study	Methods	Diagnostic method	Number of patients	Improvement rate %	Restenosis rate %	Comments
Rogers et al. ZEN Study	DES implantation in pudendal arteries	IIEF-5 Angiography	30	59,3	34,4	Patients with disseminated lesions and long-term ED were not good candidates for endovascular treatment
Wang TD et al. PERFECT -1 STUDY	Balloon angioplasty of penile arteries	IIEF-5	20	60	-	Smaller balloons were indicated because penile vessels were prone to dissection
Wang TD et al. PERFECT - 2 STUDY	Balloon angioplasty of penile arteries	IIEF-5	22	54,5	40	-
Gur S. et al.	Stent implantation and percutaneos angioplasty	SHIM	26	61	-	-
Mazo EBI et al.	Administration of PDE5I (wardenafil)	IIEF-5	122	64	-	63 % improvement rate in arteriogenic ED

This paper aims at attempting to systematize the knowledge of the benefits and drawbacks of nonsurgical endovascular treatment methods for erectile dysfunction with confirmed vascular causes.

RESEARCH REVIEW

There are few studies available concerning the vascular diagnostics and nonsurgical intervention treatment of ED. The oldest one, the ZEN Study, aimed at assessing the safety and possibility of applying drug-eluting stent (DES) angioplasty in the treatment of selected patients with an atherosclerotic etiology of ED in the internal pudental artery (IPA). Out of 383 adult men, the researchers selected 30 sexually active men (one partner at the time of the study) with a suboptimal response to PDE5I, a decreased flow in the right and left cavernosal artery (Doppler ultrasonography – DUS) and a significant stenosis in one IPA or both IPAs (visible on an angiogram). The ED intervention treatment effectiveness was assessed using IIEF-5 and SEP (Sexual Encounter Profile). Having met the ultrasonographic and angiographic criteria, the patients underwent IPA stenting with DES. The following values of a significant IPA stenosis were adopted: unilateral – ≥70%, bilateral – ≥50%. IIEF-5 was used five times. First, it was applied before and after a four-week preliminary period during which the patients had four sexual intercourses while taking PDE5I (a score of ≤21 was the basis for diagnosing ED; only the patients with scores of >6 and ≤21 were qualified for further screening). The subsequent measurements were carried out one month, three months and six months after IPA stenting. The results showed no unfavorable changes in the long-term follow-up. 45 stents were implanted in 30 patients. 59.3% of patients achieved an improvement which was measured using IIEF after three months (a score increase of ≥4) and persisted till the next measurement (after six months). The flow in the cavernosal arteries significantly increased after six months in comparison with the result of the first measurement and the one carried out a month after the intervention. A restenosis, assessed in a follow-up angiographic examination as a stenosis which narrowed the vessel by >50%, occurred in 34.4% of the atherosclerotic lesions the patency of which had been restored. The authors reached a conclusion that the use of drug-eluting stents (DES) to treat ED with an atherosclerotic etiology was safe and effective provided that the patient group was appropriately selected. They also decided that patients with disseminated lesions and long-term ED were not good candidates for endovascular treatment. They postulated further research aimed at assessing the effectiveness of that treatment method in a long-term follow-up [15].

The next study was PERFECT 1, which attempted to assess the safety and effectiveness of balloon angioplasty in ED patients with an isolated stenosis in penile arteries (unilateral: ≥70%, bilateral: ≥50%). Out of 150 patients who had undergone a computer tomography examination of pelvic vessels, the researchers selected 25 with erectile dysfunction for invasive diagnostics. Twenty men from that group who met the angiographic criteria (a max. 30 mm long lesion in a vessel with a diameter of min. 1 mm) underwent balloon angioplasty without stents. The clinical

improvement was assessed using IIEF-5 (four times). The men who obtained a score of 5–21 and had two intercourses per month with the same partner in three previous months were initially considered as leading an active sexual life despite ED. An IIEF-5 score of at least 22 after three and six months or an increase by at least 4 points in comparison with the previous score was classified as an indicator of clinical improvement. The greatest number of atherosclerotic lesions was identified in the common penile artery. No adverse events were recorded in the long-term follow-up. A symptomatic improvement was achieved in 75%, 65% and 60% of patients after one month, three months and six months respectively. The effect noted directly after the intervention was the best. An IIEF-5 score of at least 22 was recorded in 20%, 20% and 15% of patients respectively. Penile artery angioplasty as an ED treatment method in patients with an isolated stenosis in one or the same vessel proved safe and effective in 60% of patients. The authors recommended pelvic vessel angiography as a valuable examination in the precise imaging of the anatomy of atherosclerotic lesions in penile vessels. Additionally, smaller balloons were indicated because penile vessels were prone to dissection. That group of researchers also articulated the need for further studies assessing the effects of intervention treatment in a long-term perspective [16].

The PERFECT 2 Study assessed the safety and effectiveness of balloon angioplasty in ED patients with an isolated stenosis in penile arteries (unilateral: ≥70%, bilateral: ≥50%). Out of 150 men who had undergone pelvic vessel angiography and arteriography, the researchers selected 22 patients who met the angiographic criteria of inclusion in the study (a less than 40 mm long lesion in a vessel with a diameter of min. 1 mm). They underwent balloon angioplasty without stents. The procedure was effective in 91% (31 out of 34) patients. No adverse events were recorded in the long-term follow-up. One year later, the clinical improvement persisted in a half of the patients. Eight months after the procedure, restenosis was identified in 40% of men [17]. The authors reckon that the described solution seems better for penile vascularization stenoses because their diameter is smaller than 2 mm, thus excluding the use of stents. However, the 40% restenosis rate eight months after the procedure indicates the need to improve it further. Drug-coated balloons (DCB) seem a possible alternative in this case. They have been used in femoral-popliteal stenoses, yielding good results (low restenosis rates). Angioplasty is beneficial even if complicated by restenosis because the restenotic lesions measured in studies have proved shorter than the pre-angioplasty lesions, which facilitates reintervention [18].

In PERFECT 4 Study, 80% of patients immediately benefited from revascularization. A year later, however, a permanent improvement of erectile function was diagnosed only in 50–60% of the treated men. Consequently, a moderate success was recorded [19].

In the next study, von Allmen et al. [12] attempted to identify a specific pattern of damage to the arteries supplying the penis in ED patients with an incomplete response to PDE5I and CAD and/or coexisting cardiovascular risk factors in history. They examined 26 men (average age: 55) who had been sexually active with the same partner for over six months and had made four unsuccessful intercourse attempts in a month after taking PDE5I. The IIEF-5 score (≤21) pointed at erectile dysfunction. The men underwent penile artery DUS with an alprostadil injection into the corpora cavernosa and an assessment of PSV (peak systolic velocity) and EDV (end-diastolic velocity). Based on digital subtraction angiography (DSA), two groups of arterial lesions were defined: 1) macroangiopathy – a >70% stenosis in the internal iliac artery (n=10), the common iliac artery (n=2) or the internal pudental artery (n=5), which was treated via angioplasty with stent implantation or only balloon angioplasty (in the IPA); and 2) microangiopathy (in seven patients) – lesions in smaller vessels than the internal pudental artery (penile arteries with a diameter of <1 mm), with no vascular intervention. Eight patients showed no lesions in the arteries supplying the penis. The angioplasty of erection-related arteries was performed according to the commonly known procedure algorithm for critical lower limb ischemia. Small vessel stenting was avoided. Angioplasty treated 17 lesions in 11 patients; only nine men repeated IIEF-5 six months later, but their results did not improve significantly. No statistically significant changes to PSV or EDV were recorded after six months in comparison with the first measurement. As the authors concluded, nearly 40% of patients were diagnosed with macroangiopathic lesions in erection-related arteries (those were effectively treated with angioplasty), while patients with microangiopathy showed predominantly atherosclerotic lesions in the vessels above the internal pudental artery (IPA). Like their predecessors, the authors suggested the application of more adequate diagnostic methods to select an appropriate group of patients who would benefit optimally from endovascular treatment [12].

An adequate pharmacotherapy is the standard procedure in ED (PDE5I, hormonal therapy) often in combination with psychotherapy. Injections of prostaglandins into the cavernosus bodies or

urethral preparations are being used increasingly less often. Vascular interventions and penile protheses constitute the last stage of ED treatment.

The first step, even before endovascular interventions, is oral administration of PDE5I. This therapy is applied in all patients unless contraindications are present. It is relatively common that patients do not respond to treatment [11].

In relation to the above, a study was conducted to isolate groups which did not respond to PDE5I treatment. To achieve that, the researchers examined the relationship between the lesion diameter measurement results after a mechanical closure and restoration of the blood supply in the cavernosal arteries using a pressure cuff following vardenafil administration to ED patients.

The total vardenafil effectiveness in all the subjects reached 64%. The best response was achieved in the groups of patients with psychogenic ED (78%) and arteriogenic ED (63%). Five out of 15 patients with neurogenic ID

achieved a clinical improvement. Only the patients with arteriogenic ED showed a moderate positive correlation between PICAD (percent of increase of cavernosal artery diameter) following vardenafil administration and an IIEF score improvement [11].

The paper published by Swiss researchers in 2018 [17] concerned assessing the occurrence of an early elastic recoil in erection-related arteries among ED patients who underwent endovascular revascularization of the pudental artery or the penile arteries. The researchers examined 21 men insensitive to PDE5I: they excluded endocrine disorders and venous leak as ED causes and performed imaging angiography which confirmed the arteriogenic causes of the subjects' ED. The biggest number of atherosclerotic lesions was observed in pudental arteries (n=27), while fewer of them were located in the common penile artery (n=4). IIEF was applied before and three months after the procedure. The result obtained after three months was significantly better than the first one ($p<0.001$). Mild recoils (10–30%) were treated with DCB angioplasty. If a recoil exceeded 30% ten minutes after the procedure, drug-eluting stents (DES) were applied. After the intervention, all the patients took tadalafil for three weeks (daily dose: 5 mg) as well as aspirin and clopidogrel for one year. The authors have concluded that endovascular therapy of arteriogenic ED is a promising treatment alternative in a considerable group of patients. However, pudental artery recoils are frequent and might contribute to restenosis later on. Consequently, further studies are necessary to find the ideal solution for avoiding restenosis in those small ED-related vessels [20].

The researchers demonstrated a frequent relationship between common iliac artery stenosis and ED. Another study, conducted by Turkish researchers and published in 2013 [18], aimed at assessing the erectile dysfunction frequency in men with common iliac artery (CIA) stenosis and the effect of its revascularization on erectile function improvement evaluated using SHIM (Sexual Health Inventory for Men). They performed a retrospective analysis of the endovascular treatment of 36 common iliac artery stenoses in 35 men. The patients were asked if they were still interested in sex and whether they were able to recall their erectile function after stent implantation in the iliac arteries. The study included patients with chronic symptomatic CIA occlusion. However, patients aged 70 and over, patients previously diagnosed with iliac artery stenosis, acute thromboembolism or dissection as well as patients who had undergone unsuccessful rechanneling were excluded from the study. The researchers also excluded three patients who had undergone unsuccessful reperfusion. To allow erectile dysfunction diagnosis and intensity assessment, the patients filled in the SHIM questionnaire before as well as one to six months after the procedure. The erectile function improvement or deterioration was assessed based on SHIM score changes in subsequent measurements. The average age of the patient population was 57 ± 5 (range: 42–67). The most frequent atherosclerosis risk factors were: smoking in history (86%), diabetes (37%), coronary artery disease (64%), hypertension (44%) and hyperlipidemia (46%). All the patients showed symptoms of chronic intermittent claudication. Occlusions and stenoses of the iliac arteries were effectively treated with stent implantation or percutaneous angioplasty. The average occlusion length was 59 ± 41 (range: 10–180) mm. The impotence rate reached 74% (26 out of 35) before the procedure. In general, 16 (61%) out of 26 patients reported an erectile function improvement after iliac artery rechanneling. According to SHIM, the improvement was complete in six patients (17%), satisfactory in nine patients (26%) and moderate in one patient (3%). The rechanneling type, the patient's age and the occlusion length were related to ED improvement in a one-way analysis. However, those did not constitute independent factors of an erectile function improvement in a multivariate analysis. All the patients in the group with combined occlusions of the external iliac artery and the common iliac artery (n=5) showed mild to severe impotence. Bilateral stenoses in the internal iliac artery (IIA) were rechanneled and ED was successfully treated in three of them. The two remaining patients also showed bilateral IIA occlusions: erectile dysfunction subsided in one of them and remained unchanged in the other. Operative and postoperative complications occurred in eight patients (23%). Serious procedure-related complications included artery dissections which caused a significant stenosis or closure of the ipsilateral artery near the treated section (n=3) and an internal iliac artery occlusion caused by common iliac stenting (n=1). All the flow-limiting foci were effectively treated via endovascular reintervention [21].

The summary results of described research studies were shown in table 1.

LIMITATIONS OF THE CITED WORKS

Important limitations of all the abovementioned studies include: small study groups, lack of a control group and low-specificity noninvasive methods of assessing the clinical improvement. Only von Allmen et al. examined their patients after angioplasty using digital subtraction angiography (DSA), which is presently the gold standard in assessing penile vascularization lesions. Moreover, only single stenoses were revascularized in most studies, which does not answer the question about procedure effectiveness for total occlusions and long tandem stenoses. According to the authors of the PERFECT 1 Study, not all the patients underwent invasive angiography. Some of them underwent only a CT angiography of pelvis, which is a less precise examination. Consequently, the number of restenoses may have been overstated.

An analysis of the ZEN Study planning reveals several inconsistencies. After the four-week treatment with sildenafil, the patients who did not react to it or whose response was suboptimal were all qualified as nonresponding to treatment. The authors made a mistake by failing to describe the earlier outcomes of PDE5I treatment, so the picture of the response to the applied treatment was not reliable [15, 22]. The decision to apply DES in the treated patients

was made based on an assumption that the smaller vessels in the pudendal artery vascularization responded to zotarolimus as did the smaller coronary arteries and thus restenosis would be prevented. However, 34.4% (11 out of 32) of the rechanneled lesions were affected by restenosis, which is a considerable percentage compared to the average restenosis frequency in the coronary arteries (9.2%). For unknown reasons, zotarolimus is less effective in the treatment of lesser pelvis arteries [22]. Balloon angioplasty in the PERFECT 2 Study yielded a 40% restenosis rate after eight months. That percentage is comparable with the rate obtained by the balloon angioplasty of popliteal arteries and most peripheral vessels [20]. The authors pointed at the possibility of improving those results by using DES, but the actual improvement rate was less than 6%. A drawback of using DES is the necessity of double antiplatelet therapy, which was not mentioned in the ZEN Study. The risk–benefit ratio for the necessity of double antiplatelet therapy following DES implantation seems obvious in CAD treatment, but is doubtful when using DES to treat ED. Only pelvic vessels were stented in the ZEN Study. Penile vessels cannot be made patent using stents because their diameters are too small: the penile artery diameter is <2 mm, while the smallest stent diameter available is 2.0 mm, and excessive stretching of a vessel results in an intensified restenosis. The stent breakage risk during sexual activity must also be taken into account [20]. Moreover, the ZEN Study disqualified patients with coexisting venous drainage disturbances (EDV >5 cm/s), therefore excluding a possible cause of the failure to obtain the anticipated effects of endovascular treatment.

One should mention that there is a specific group of patients who may benefit from this method of artery patency restoration in the lesser pelvis: young men after blunt traumas to the lesser pelvis. Arterosclerosis rarely is the cause of ED in 30- 40- year- old men. However, endovascular treatments could be useful in some circumstances. The stenosis development mechanism in this patient group is based on two phenomena. First, a trauma causes vascular endothelial dysfunction which drives the atherosclerotic process resulting in stenoses. The second phenomenon is of an anatomical origin: the distal IPA running through Alcock's canal is extremely exposed to a blunt trauma and the pressure exerted by the ischiopubic branch [22]. The method proposed in the ZEN Study may prove the perfect solution for treating difficult cases which feature focal atherosclerotic lesions caused by the trauma in question [22].

The significant limitations of the study conducted by von Allmen et al. include the presence of other, nonvascular factors influencing the erectile function: 46% of the patients were taking beta-blockers [12].

60% patients in the study described by Turkish researchers noted an erectile function improvement following endovascular procedures [21]. Still, this study also has several limitations. First, it involved a small group which restricted the statistical analysis. Second, it seems that an ED assessment based only on a questionnaire, even an anonymous one, may be distorted by lack of consistency or honesty in the answers. Psychological and functional causes of erectile dysfunction cannot be reliably separated either. The use of preoperative and postoperative SHIM questionnaires did increase the value of that study, but combining such application of those questionnaires with an objective assessment of erection using PBI (penile brachial index), duplex ultrasonography or angiography may create a more precise method of examining the real effect of endovascular therapy on erectile function. The same objections concern the use of IIEF-5. On the other hand, endovascular rechanneling and stenting of CIA occlusions may be an effective therapy, particularly in order to maintain or improve erectile function. A return to normal sexual function may be achieved via endovascular therapy of the CIA in patients with impotence of a vascular origin, without any psychogenic factors affecting erection, with distal artery damage and without a coexisting distal obstructive disease in the pudental or penile arteries. An assessment of patients with Leriche syndrome or iliac artery aneurysms should include a detailed interview concerning sexual functions.

One must also mention the surgical treatment of the veno-occlusive mechanism insufficiency in the corpora cavernosa of the penis. The possibility of preventing blood outflow from the penis and therefore maintaining a satisfactory erection is as important as an appropriate blood inflow [22]. However, urologists commonly view venous leak as a sign and not a cause of erectile dysfunction [24]. This aspect of ED treatment goes beyond the scope of the present paper though.

DISCUSSION

Intervention treatment of erectile dysfunction consists in the application of an appropriate endovascular method depending on the vessel type undergoing revascularization. The most common methods include balloon angioplasty and angioplasty with stent implantation in the erection-related arteries, i.e. those which supply blood to the penis. This treatment method requires selecting an appropriate group of patients who meet specific qualification criteria. Patients with disseminated atherosclerotic lesions, difficult vascular access for anatomical reasons and fixed erectile dysfunction as well as the coexistence of other, hard-to-eliminate causes will not benefit from this treatment method. Few studies concerning vascular diagnostics and nonsurgical intervention treatment of erectile dysfunction in patients with an insufficient response to PDE5I have been published thus far. No serious adverse events were noted in long-term follow-ups: the method proved safe to those patients. Treatment effectiveness was assessed using standard forms, most often the International Index of Erectile Function. In some studies, nearly 60% of patients achieved an improvement as measured using that test several months after the procedure. However, the restenosis rate turned out to be higher than the one for coronary vessel patency restoration. No procedure standards have been prepared yet and it remains unclear

who should perform the revascularization procedures in erection-related arteries: an angiologist, a vascular surgeon, a urologist or a radiologist. Unlike surgeries, endovascular procedures do not entail the risk of nerve damage, but they may lead to the formation of microthrombi in the rechanneled vessels. Taking into account both the benefits and limitations stemming from this modern treatment method, the authors of the present paper recommend caution and moderate optimism.

One must not forget other, nonvascular erection-affecting factors which coexist with vascular causes, e.g. taking specific drugs, endocrine disorders or psychogenic factors, which have an enormous influence on the assessment of clinical improvement. To assess the effectiveness of erectile dysfunction treatment in a special population of patients among the men encumbered with cardiovascular risk factors using this method in a long-term follow-up, it is necessary to conduct randomized studies on larger patient groups [25].

CONCLUSIONS

Peripheral vascular atherosclerosis plays a significant role in erectile dysfunction development. Endovascular procedures in erection-related arteries are safe in a specially selected group of men. It is necessary to conduct further studies to define an appropriate group of patients who have a chance of benefiting optimally from endovascular treatment in a long-term follow-up. It is also necessary to use more adequate tools to assess the clinical state.

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ORCID and contributionship

Magdalena Piegza – 0000-0002-8009-7118 [A-B,D-F]
Mateusz Paterak – 0000-0001-7843-6355 [B,D-F]
Michał Błachut – 0000-0002-4438-2376 [D-F]
Jacek Piegza – 0000-0002-7356-4769 [A,D,F]

Conflict of interest

Authors declare no conflict of interest

CORRESPONDING AUTHOR

Mateusz Paterak
Student Scientific Society at Chair and Department of Psychiatry in Tarnowskie Gory,
School of Medicine with the Division of Dentistry in Zabrze,
Medical University of Silesia in Katowice, Poland;
tel.: 886714761
e-mail: mateusz.paterak1@gmail.com

Received: 16.07.2020
Accepted: 12.09.2020

REVIEW ARTICLE

REPRODUCTIVE CHOICE: INTERNATIONAL ETHICAL STANDARDS AND PROSPECTS FOR LEGAL REGULATION IN CERTAIN EUROPEAN COUNTRIES

DOI: 10.36740/WLek202009230

Kateryna V. Nykolyna
TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, KYIV, UKRAINE

ABSTRACT

The aim: The article is aimed at elucidating the prospects for the formation of universal ethical and legal standards in the work of medical workers in order to ensure the reproductive choice of a person according to the analysis of international documents, court practice of the ECHR, and the national legislation of individual European countries.

Materials and methods: Research materials include scientific developments of both domestic and Western theorists and human rights defenders in the field of medical law in the aspect of reproductive choice. The recommendations of the Center for Reproductive Rights in the USA, the World Health Organization, the United Nations, and the ECHR practices were of great importance. This article used the methods of searching, analyzing, organizing, and summarizing information.

Conclusions: It is necessary to ensure the provision and guarantee of reproductive choice for everyone at the level of the Constitution. Given the public debate about the contradictions of individual manifestations of reproductive autonomy, it is proposed at the first stage of legal regulation to develop national principles and ethical standards for medical workers in this area.

KEY WORDS: reproductive choice, informed consent, post-mortal reproduction, reproductive rights

Wiad Lek. 2020;73(9 p. II):2067-2074

INTRODUCTION

One of the main achievements of the second half of the XXI century was the development of science, technology, and production. However, the twentieth century is not only marked by the highest achievements in science but also a fundamental rethinking of what the human body is, what its status is, and what the boundaries of everyone's physical freedom are. In fact, the world is moving into the realities of a new socio-legal paradigm. A person's desire at the right moment of one's life to consciously escape from suffering, to improve or change one's body with medical technologies, to recreate one's essence by cloning or to model one's own body in a nonmetric form of objective existence, etc gave rise to a new legal phenomenon - somatic human rights (from the Greek soma - body). These human rights to free use of the body arose not only in the last two centuries: specific issues concerning the human right to homosexual contacts, prostitution, and sterilization have long been interested for legal science, but due to their specificity, they were always outside the law, outside of society, and its moral and ethical standards.

This year marks two important dates in the history of reproductive health: 50 years since the start of activities of UNFPA and 25 years since the time of conduction of the momentous event - the International Conference on Population and Development (ICPD) in Cairo. The 2019 population health report reflects the current state of sexual and reproductive health and rights 50 years after the establishment of the United Nations Fund for Population Activities (UNFPA). "During this time, the collaborative efforts of civil society, governments, development agencies, and UNFPA have opened up new perspectives and opportunities for women and girls around the world. Nevertheless, we still have a long way to go before all women and girls will use the real opportunity and the means to allow them to manage their own body and make informed decisions about protecting their sexual and reproductive health," Natalia Kanem, Executive Director of UNFPA says in the preface of the report [1].

An important component of ensuring reproductive human rights is the guarantee of free reproductive choice (reproductive autonomy) of couples or individuals to freely and responsibly choose the time, number and interval between their children [2]. The development of medical and biotechnology today creates new challenges for the ethical and legal regulation of the right to manage one's reproductive health. This also includes post-mortal (post-mortem) reproduction, the use of assisted reproductive technology for persons of ripe years, for HIV-infected parents, and others. However, as noted in the medical literature, when trying to formulate universal international standards for applying the right of free reproductive choice, certain contradictions between demographic priorities and reproductive choice and contradictions between the universal concept of human rights and national customs/religion arise [2].

THE AIM

The article is aimed at elucidating the prospects for the formation of universal ethical and legal standards in the work of medical workers in ensuring the reproductive choice of a person according to the analysis of international documents, court practice of the ECHR, and the national legislation of individual European countries. The task is to develop scientific and practical proposals for legal regulation in certain countries of Europe in the specified sphere of public relations.

MATERIALS AND METHODS

As for the materials used, among them, there are relevant scientific developments of both domestic and Western theorists and human rights defenders in the field of medical law. The materials of the Center for Reproductive Rights in the USA, the World Health Organization, and the United Nations are important for the analysis. Since reproductive rights are part of human rights, the international human rights standards set forth in the conventions and the practice of the ECHR are the material basis of the study.

REVIEW AND DISCUSSION

Reproductive healthcare providers must take into account not only the ethical considerations inherent in their work but also human rights standards regarding reproductive rights. The difficulty lies in the fact that the development of these standards is faced with certain problems.

The foundations of the concept of reproductive rights were laid in 1968 at the Tehran International Conference on Human Rights, when they recognized the right to freely, with a sense of responsibility, determine the number of children and the time of their birth [3]. In paragraph 7.2 of the Program of Action of the International Conference on Population and Development, which was held in Cairo on September 5-13, 1994, it was noted that reproductive health is not just evidence of the absence of diseases of the reproductive system or impaired function, but it is a state of complete physical, mental, and social well-being, which provides for the possibility of a satisfactory and safe intimate life, the ability to reproduce, the right of men and women to information and access to safe, effective methods of family planning and other contraceptive methods that they choose, which do not contradict the law, as well as the right to access to appropriate health care services, which allow a woman to safely endure pregnancy and childbirth and parents to create the best conditions for the birth of a child. However, not all states have accepted the inclusion of reproductive rights as part of internationally recognized human rights. At the Cairo Conference, several countries (usually for religious reasons) expressed official warnings regarding the concept of reproductive rights or its specific content [4].

The issue of reproductive rights was further developed in paragraph 95 of the Program of Action, which was approved by the Fourth World Conference on Women in Beijing on September 4-15, 1995. This act states that reproductive rights are based on a set of fundamental rights: all married couples and individuals freely can make a responsible decision regarding the number of children, the intervals between their birth, the time of their birth and possess the necessary information and means for this; rights to achieve the highest possible level of sexual and reproductive health, including the right to make decisions on issues related to reproductive behavior in the absence of discrimination, coercion, and violence; to receive information and access to safe, effective family planning methods and related health services [5].

Unfortunately, some conservative political and religious forces continue to stand against certain means of protection and promotion of reproductive rights. Access to contraceptives, although not always explicitly prohibited, is not adequately provided in some countries. Legal abortion in most European Union countries has been largely liberalized by legislative and judicial decisions, however, there are legal obstacles in some countries [6].

The World Health Organization defines reproductive rights as follows: Reproductive rights are based on the recognition of the fundamental right of all couples and individuals to freely and responsibly determine the number of their children and intervals of their births, as well as to have the information and means to do so, as well as the right to attainment of the highest sexual level and reproductive health. They also include the right of all people to make decisions on reproduction without discrimination, coercion, and violence [7].

From this definition it is logically possible to distinguish basic reproductive human rights: the right to freely choose the number of children and the time of their birth (including the right to refuse the birth of children); the right to information to achieve the highest level of reproductive health; the right to obtain means to achieve the highest level of reproductive health (including access to reproductive technologies); the right to the reproductive choice.

Reproductive choice (or reproductive autonomy) is an opportunity to make decisions independently about one's own reproduction, free from discrimination, coercion, or violence.

However, the biggest problem is that there is no detailed legal regulation of reproductive rights, both at the national and international level. To date, this area of public relations is governed by the documents adopted at the World Conferences and the Convention on Human Rights for Biomedicine. The European Convention for the Protection of Human Rights and Fundamental Freedoms is of particular importance. Despite the fact that none of its articles directly regulates reproductive rights, however, the ECHR has developed a fairly broad practice in protecting them using Articles 2, 8, 12 (right to life, right to respect for privacy and family life, non-discrimination).

Attempts to consolidate the definition of "reproductive rights" and to improve the legal regulation of relations in the sphere of their exercise have been also made in Ukraine. In February 2004, a draft law of Ukraine "On Reproductive

Rights and Guarantees of their Exercise" was developed [8]. Strong objections to its adoption were raised by religious communities and organizations. In July 2005, a draft law on Reproductive Health [9] also sparked much debate. It should be noted that as of 2019, there is no single legislative act in Ukraine that would specifically, comprehensively and clearly enshrine the reproductive rights of an individual, determine their specificities, and guarantees of exercise.

DISCUSSION

The absence of legal regulation of the exercise of rights in the Institute of Reproductive Technologies is not clearly regulated in national legislation. The lack of thorough studies at the national level in this area is explained by the fact that the widespread use of artificial insemination methods and, consequently, reproductive technologies is not widely known to the public. In addition, in Ukrainian society, as in some other countries in Europe, the support of traditional family values and Christian morality prevail, as a result, interventions in the reproductive field are treated with caution and sometimes considerable criticism.

However, the right to reproductive autonomy is an integral part of the right to health and therefore cannot be denied as a natural human right. People are free and no one can be compelled to do or refrain from committing actions other than on their own free will. And the medical field is no exception. Any medical intervention, including in the reproductive field, should be carried out with the consent of the individual only.

Reproductive choice (autonomy) should be based on the informed consent concept, which is to inform the patient of all possible risks of diagnosis, treatment, or abstention from medical intervention, and to express the patient's consent. Informed consent can be understood as a requirement of respect for the right to self-determination as a means of ensuring personal freedom [10].

The problem of reproductive choice also arises in the context of post-mortem reproduction. At present, this issue is being actively discussed in medical science [11]. The particularly relevant question: Is it possible to consider the right of the wife/close relatives to use the deceased's reproductive material as part of the right to reproduction? In the context of the military conflict in Ukraine, when many soldiers die, the answer to the question becomes crucial for their wives. To date, only the US and Israel have a legislative provision about the mandatory collection of biological reproductive material from military personnel sent to the war zone.

Today, there are several options for posthumous reproduction: the use of cryopreserved sperm (or ovum) taken during a person's life or the transfer of previously frozen embryos, as well as a completely new direction - the posthumous removal of sperm of a deceased man. If everything is clear with the first two methods, then post-mortem sperm collection raises a huge number of both medical and ethical-legal issues. First of all, it is possible to do by the method of electro-ejaculation, which stimulates the ejaculatory mechanism of the deceased man. It uses TESE (testicular sperm extraction), PESA (percutaneous epididymal sperm extraction, i.e. through the skin, sperm collection from the epididymis), and TESA (percutaneous aspiration of sperm from testicular tissue) technologies. In addition, the testicles of a man may be posthumously removed to obtain sperm. Regardless of the type of application of the technique, sperm collection should be carried out within 24-36 hours after the death of a man, immediately after which the sperm is cryopreserved for further use in the protocol of assisted reproduction technologies. And here the problem arises: how to establish whether the deceased agreed to such a collection of reproduction material: Can the reproductive choice be made by his wife/close relatives?

In some states (Germany, Denmark, France, Switzerland, Sweden) posthumous reproduction was prohibited, and in a number of countries (Belgium, Great Britain, Israel, the Netherlands, USA, etc.) it is carried out legally [12].

Taking into account foreign experience, one should agree with the proposal to establish at the level of national legislation (for states that do not prohibit post-mortal reproduction) the form for obtaining the donor's consent to use reproductive material after death, to define a clear circle of persons entitled to such a use, to establish the status and the inheritance rights of the child born as a result of such a reproduction [13]. In addition, it should be borne in mind that the period during which it is possible to perform posthumous removal of reproductive material is very limited in time. Involvement of the judiciary to decide on the presence or absence of prior consent (if it was not recorded in writing) will not always be appropriate, since the duration of the trial, as a rule, exceeds the necessary 24-36 hours for the collection of biological material. Obviously, in this case, it is necessary to develop detailed medical protocols, in which the mechanism for establishing the prior consent of the deceased should be clearly defined.

Separately, the issue of reproductive autonomy of the disabled should be raised. In the healthcare sphere, they face many discriminatory practices. Women and girls with disabilities are especially vulnerable to forced medical intervention in reproductive health [14]. In this context, the provisions of the Convention on the Rights of Persons with Disabilities should be implemented in national legislation as ethical and legal standards. It was ratified by Ukraine on December 16, 2009, and reaffirms the rights of women and girls with disabilities to reproductive autonomy, including autonomy related to reproductive health, along with persons without disabilities.

The importance of legislative consolidation of such a right is that it will protect patients with disabilities from the psychological pressure of medical workers aimed at refusing to give birth to children. This is precisely the problem that concerns the Ukrainian married couple with cerebral palsy, who became parents in 2017: "We really wanted a child. I knew that asking the doctors for permission didn't make sense - they were unlikely to allow doing that. Therefore, when I became pregnant, I did not go to the maternity welfare center immediately. I felt that the

child was developing well. Then, of course, I often heard: "how do you carry pregnancy to term with your bunch of diseases"? I went on bed rest, but the attitude of the doctors was bad. I left the hospital on the third day and led an active lifestyle until the very birth. I understood that the health of the child is in my hands "[15]. Thus, the lack of proper legal regulation in this area leads to the growth of a large number of problems with the procedure for applying guarantees of reproductive choice.

However, to be fair, it is worth noting that on February 7, 2019, two alternative draft laws on reproductive rights "On assisted reproductive technologies" were registered in parliament. The authors proposed establishing at the legislative level the determination of the definitions of infertility, donation of oocytes (ovum), sperm, embryos, a reproductive cell donor, surrogate maternity (surrogacy), reproductive cells and tissues, etc. The importance of such a legal regulation lies not only in protecting the rights of patients, but also in securing guarantees for medical workers. Legislative regulation is the basis for the development and approval of national medical protocols for the use of reproductive technologies.

The analysis of the existing legal regulation indicates that the provision of the right to reproductive technology is connected exclusively with medical indications and is considered by the legislator only as a method of treatment of infertility. However, today, there are situations when assisted reproductive technologies can be applied in non-treatment cases. As a result of the increase in the number of natural disasters, cancer diseases, mortality in the war zone, relatives and spouses of the dead are increasingly turning to doctors to "create" a new life, posthumously using the genetic material of a person close to them. It is clear that when making such a decision, the interests of all parties should be taken into account: the deceased parent (s), the party initiating the protocol of artificial insemination (husband/wife, parents or close relatives of the deceased) and the future child.

However, when it comes to the question of the need to fully consolidate these rights, one should turn to the relation between law and bioethics. Thus, the Ukrainian scientist M. Medvedeva, who deals with the issues of somatic human rights, identifies three models of the interaction of ethics and law: sociological (under which the right is not able to solve complex ethical dilemmas and is not the main regulator of such a public relation), formalistic (the right plays the leading role in the regulation of all bioethical issues), and liberal (the law enshrines only some bioethical principles) [16].

We believe that the development of somatic human rights will depend on which model for the regulation of bioethical issues will be chosen by society and the state. It should be noted that not all scientists and practitioners support the legislative consolidation of somatic human rights. In general, the admissibility of a particular practice by law signals to people that this practice is clever (though in certain circumstances) despite the fact that previously this could be considered inadmissible [17].

Evidence of a violation of the right to reproductive autonomy is the ECHR's classic citation in Case "Tysiak v. Poland" under No. 5410/03 dated 24 September 2007. The applicant was refused to do a therapeutic abortion after being warned that her severe form of myopia could worsen if she carried pregnancy to term. Immediately after the birth of the baby, her retina started to bleed, which made her a disabled person.

The European Court of Human Rights found that the applicant had been denied the right to access effective mechanisms that could determine whether the conditions for legal abortion were in breach of Article 8 (right to respect for private and family life) of the European Convention on Human Rights [18].

The similar situation in Ireland illustrates the case considered by the ECHR on application A., B., and C. v. Ireland (application no. 25579/05) dated December 16, 2010. Three women living in Ireland who became pregnant unintentionally contested the fact that due to their inability to perform a legal abortion in Ireland, they had to travel to the United Kingdom. The applicants noted that this procedure was humiliating, shameful, and risky to their health. Performing or assisting anyone with abortion is a criminal offense in Ireland. However, there is a constitutional right to abortion if there is a real and significant risk to the mother's life. One of the applicants, who was in remission of a rare form of cancer and was unaware of her pregnancy, was being treated. The Court held that Ireland had failed to secure the applicants' constitutional right to legal abortion. Thus, Article 8 (right to respect for private and family life) of the Convention was violated. The court noted that the ambiguity about the determination of the woman's pregnancy posed a threat to her life and the threat of prosecution of medical professionals had a significant impact on the decision of the doctors [19].

Nowadays, one of the reasons for the abuse of reproductive rights is expressed in the modern medical literature - the existence of gender stereotypes. For example, in a new study, "The Impact of Gender Stereotypes on Human Rights in the Context of Reproductive Health", Chiara O'Connell and Christina Zampas justify the existence of a stereotype about women's vulnerability and inability to make decisions about their health. Instead, men and people in leadership positions, such as physicians who perform medical procedures, male members of the family, or society as a whole, are more empowered to make decisions for women.

This stereotype acts so that women are denied information to make reasoned decisions about their reproductive health and replace the decisions of others with their own [20]. We are talking about "paternalistic control" by doctors, who, using medical knowledge and abusing medical terms, actually make decisions instead of the patient. In the aspect of reproductive rights, such an effect may consist of not providing a woman with complete information about alternative options (for example, to continue or terminate a pregnancy) [21].

Given the possible negative consequences for both the physical and psychological health of a woman, we suggest

reinforcing the obligation of healthcare professionals to provide written explanations to the patient of its reproductive rights in each case. Rebecca Cook also emphasizes this role of the physician, noting that it will facilitate the consolidation of individual choice and not distort it [22]. To address this problem, FIGO has developed and issued ethical standards "Harmful stereotyping of women in health care», recognizing the harmfulness of stereotypes about women in health care, and giving recommendations to obstetricians and gynecologists on identification and avoidance of the stereotypes of both patients and colleagues [23].

The legislative concept of the informed consent or the right to make informed choice for one's own future requires that health professionals would refrain from paternalistic control and instead provide women with the information, which is not coercion or personal preferences. The definition of the informed consent of the International Federation of Gynecologic and Obstetric Institutions states: "It is important to remember that informed consent is not a signature but a process of communication and interaction. […] If doctors, due to their own religious or other beliefs, do not want to fulfill the criteria of the informed consent because they do not wish to provide information about certain alternatives, they have an ethical obligation, in respect to their patients' rights, to open their objections and to take appropriate directions, while respecting the rights of their patients, open their objections and make appropriate referrals so that patients can obtain the full information they need to make free and informed choices"[24]. We believe that these recommendations must be implemented in the national system of law when adopting legislation in the field of reproductive rights.

Social progress can not be stopped by artificial restraint, and since there is a demand for certain rights that a person cannot exercise without state authorization (often as a result of outright prohibition of such actions), they have to find their own legislative consolidation sooner or later. In today's world, people are given more opportunities, but as a result of increasing responsibility for their lives, they have to choose these opportunities independently and responsibly. It is the duty of the state to give the society the rights it requires and the real mechanism for their implementation; it is the duty of the society and the individual to realize the consequences of such changes and to put them or not to put them into life.

CONCLUSIONS

To summarize, we can draw some conclusions and generalizations:

1. States, depending on the level of legal regulation of reproductive rights, can be conditionally divided into: liberal, which provide broad reproductive rights and provide free reproductive choice (USA, Belgium); paternalistic, which, because of religious influence and national traditions, significantly limit their reproductive choices (Islamic countries, Ireland, Croatia); those, which do not have legal regulation of reproductive choice (Ukraine, Russia).
2. The lack of legal regulation of reproductive choices and reproductive rights significantly complicates their implementation and protection.
3. Given the considerable public and scientific discussions regarding a clear list of reproductive rights and their scope, due to the influence of religious organizations and the support of traditional family values, in some European countries (Ukraine, Poland, Croatia, Hungary, etc.), it is proposed in the first stage to consolidate guarantee of their provision by the state at the level of the Constitution.
4. In the next stage, it is proposed to develop a Concept for the development of national legislation in the field of reproductive rights, taking into account ethical and legal international standards and to consolidate the following principles: freedom of reproductive choice; equal access for men and women to reproductive technologies; non-discrimination in the field of reproductive rights; tolerance of health professionals in relation to all groups of patients; insurance of the confidentiality and privacy in the application of reproductive technologies; responsibility for violation of free reproductive choice.

Of course, reproductive rights have arisen in connection with the public need and rapid development of medicine, biology, and chemistry. However, along with all the useful novelties that bring scientific and technological progress, significantly improve the standard of living, and create opportunities, which the society has not previously been able to use, the active development of such rights (including the state authorization of negative aspects of such rights) can lead to unheard-of consequences, after which the condition of the human society will no longer be able to return to its primary condition. In addition, this category of rights is quite specific and, at present, the theoretical paradigm of its functioning has not yet been fully formed. There are a number of questions before humanity that must be answered before these rights can coexist with previous generations of rights.

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ORCID and contributionship:
Kateryna V. Nykolyna: 0000-0002-8603-1013 [A, B, C, D, E, F]

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Kateryna V. Nykolyna
Taras Shevchenko National University of Kyiv
60 Volodymyrska St., Kyiv 01601, Ukraine
tel: +380673179205
e-mail: nykkatya@gmail.com

Received: 14.10.2019
Accepted: 23.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

IMPLEMENTATION OF THE ECOSYSTEM APPROACH AS A NECESSARY CONDITION FOR ENSURING THE CONSTITUTIONAL HUMAN RIGHT TO A SAFE ENVIRONMENT FOR LIFE AND HEALTH

DOI: 10.36740/WLek202009231

Yevhenii P. Suietnov
YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: Is to study some aspects of the formation of the ecosystem approach, develop on its basis the latest and promising area of scientific research – EcoHealth and determine the legal framework for the implementation of this approach in Ukraine.

Materials and methods: The research is based on international legal documents, statistical reports and information of the WHO, practice of the ECHR, constitutional acts of foreign countries, legislation of Ukraine, works of scientists on ecology, medicine, environmental and medical law. For achievement of reliable and objective results general philosophical (dialectical), general scientific (historical, analysis and synthesis, analogy) and special (comparatively-legal, interpretation of legal norms) methods of scientific knowledge were used.

Conclusions: A necessary condition for ensuring the constitutional human right to a safe (favorable, benevolent, healthy, etc.) environment for life and health and, consequently, the right to life and health, is the implementation of an ecosystem approach into national strategies and legislation of different countries, including Ukraine. The development of this approach at the international level has led to the emergence of a new area of scientific research – EcoHealth, which studies how changes in the Earth's ecosystems affect human health. In Ukraine, the issue of implementing an ecosystem approach to health is not widespread in the scientific literature yet, but this trend is clearly visible in environmental legislation.

KEY WORDS: the right to life and health, the right to a safe environment for life and health, the right to a favorable environment, ecosystem, ecosystem approach

Wiad Lek. 2020;73(9 p. II):2073-2080

INTRODUCTION

Human life and health depend on the quality and safety of the environment in which they live. According to WHO, roughly 12.6 million people die every year from environment, which is 23% of all deaths in the world [1]. Among the environmental risks are air, water and soil pollution, ultraviolet and ionizing radiation, climate change, hazardous waste, chemical and biological substances, etc., while the main deadly diseases caused by contaminated ones are such diseases as stroke (2.5 million), ischaemic heart disease (2.3 million), unintentional injuries (1.7 million), cancer (1.7 million) and chronic respiratory diseases (1.4 million) [2].

Environmental risk factors are also recognized as a global cause of child mortality, as they kill 1.7 million children under the age of five each year, representing more than a quarter (26%) of deaths at that age [3]. "A healthy environment underpins a healthy population," says Dr. Margaret Chan, WHO Director-General. "If countries do not take actions to make environments where people live and work healthy, millions will continue to become ill and die too young." [4]. Therefore, it is obvious that the right of every person to life and health is inextricably linked to right to a safe and healthy environment, the adequate ensuring and protection of which is an urgent necessity of today.

In accordance with Article 3 of the Constitution of Ukraine, human life and health are recognized as the highest social value. This constitutional norm is specified in other articles of the Fundamental Law of Ukraine, in particular in Article 27, under which every person has the inalienable right to life, the protection of which is the duty of the State, and Article 49, which proclaims everyone's right to health protection, medical care and medical insurance. Regarding the right to a safe environment, it is enshrined in Article 50, according to which everyone has the right to an environment that is safe for life and health, and to compensation for damages inflicted through the violation of this right.

Unlike Ukrainian legislation, which uses the term "the right to a safe environment", the international legal documents, acts of the EU and the legislation of other countries enshrine the right to "a favorable environment", "a benevolent environment", "a healthy environment", etc. For example, the Constitution of the Republic of Latvia declares that "the State shall protect the right of everyone to live in a benevolent environment" (Article 115); according to the constitutions of Hungary and Belgium, everyone has "the right to a healthy environment" (Article XXI and

Article 23, respectively); the Constitution of the Republic of Bulgaria admits for everyone "the right to a healthy and favorable environment" (Article 55).

The human right to a safe (favorable, benevolent, healthy, etc.) environment is also ensured by the norms of the Convention for the Protection of Human Rights and Fundamental Freedoms (1950), better known as the European Convention on Human Rights. Although the Convention does not have a particular article on this right, however, according to the practice of the European Court of Human Rights, in case a person applies for protection of the violated right, the ECHR considers and decides the case, guided by Article 8 of the Convention, which proclaims that "everyone has the right to respect for his private and family life, his home and his correspondence". It is on the basis of this Article that the ECHR issued a number of decisions in cases both with regard to foreign states and Ukraine (in particular, "Lopez Ostra v. Spain", "Giacomelli v. Italy", "Hatton and Others v. the United Kingdom", "Fadeyeva v. Russia", "Dubetska and Others v. Ukraine", "Grimkovskaya v. Ukraine", etc.).

An analysis of the main documents on the protection of environment, life and health gives reason to assert that the human right to a safe (favorable, benevolent, healthy, etc.) environment for life and health and, consequently, the human right to life and health is inevitably linked to the conservation and restoration of natural ecosystems, which should be carried through the implementation of an ecosystem approach.

THE AIM

The aim of the research is to study some aspects of the formation of the ecosystem approach, develop on its basis the latest and promising area of scientific research – EcoHealth and determine the legal framework for the implementation of this approach in Ukraine.

MATERIALS AND METHODS

The research is based on international legal documents, statistical reports and information of the WHO, practice of the ECHR, constitutional acts of foreign countries, legislation of Ukraine, works of scientists on ecology, medicine, environmental and medical law. For achievement of reliable and objective results general philosophical (dialectical), general scientific (historical, analysis and synthesis, analogy) and special (comparatively-legal, interpretation of legal norms) methods of scientific knowledge were used.

REVIEW AND DISCUSSION

The central category of the ecosystem approach is the ecosystem (from Greek οἶκος – housing, location and σύστημα – combination, association) – a set of living organisms and the conditions of their existence, which are in a natural interconnection with each other and form a system of mutually-conditioned biotic and abiotic phenomena and processes. It is well known that the term "ecosystem" was introduced into scientific use by the English botanist and a pioneer in the science of ecology A.G. Tansley, who wrote in the book "The use and abuse of vegetational concepts and terms" (1935) about the impossibility of separating organisms from their special environment, with which they form one physical system. These ecosystems, as we may call them, are the basic units of nature on the face of the earth and they are of the most various kinds and sizes [5].

Later in the scientific literature, other definitions of the ecosystem were developed and justified the dependence of human life on the stable functioning of ecosystems. According to E.P. Odum, considered the father of modern ecology, an ecosystem is any entity or natural unit that includes living and nonliving parts interacting to produce a stable system in which the exchange of materials between the living and the nonliving parts follows circular paths [6]. In another publication the scientist writes that the ecosystem is the main functional unit of ecology, as it includes both organisms (biotic communities) and the abiotic environment, with each of these parts influencing the other and both necessary to sustain life as it exists on Earth. And emphasizing the importance of careful study and conservation of ecosystems, he notes that approaches to the study of ecosystems must be translated into an action program if people are to survive the current environmental crisis that they themselves have created [7].

Modern environmental scientists, including V.I. Danilov-Danilyan, V.I. Losev and I.E. Reyf, speak out on this problem no less eloquently. It is significant, they write, that not only people who are far from science, but also many environmentalists have not yet realized what is the central point of global environmental changes that have occurred over historical time, and especially over the past 50-100 years, as a result of environmentally destructive economic development and unbridled demographic growth. This is not the pollution of the environment, which affects the majority of the world's population. And it is not climate warming, whose connection with the greenhouse effect is still being questioned by some researchers. The main environmental outcome of human economic activity is the destruction of natural ecosystems in vast land areas as well as in the water areas of semi-enclosed seas and the coastal oceanic zone. It is the sharp weakening of the environment-forming and stabilizing functions of biota on large territories that threatens the biosphere with the most catastrophic consequences. And only reliance on natural forces, on the natural potential of living biota can, perhaps, prevent the worst option for further development – demographic collapse, population decline, erosion of the foundations of modern civilization, etc. In general, the destruction or deformation of natural ecosystems as a result of human activities is undoubtedly the most important and essential aspect of the global environmental crisis [8].

Considering the functions of ecosystems in nature and their importance for maintaining its favorable condition, the problem of preserving and restoring ecosystems in order to ensure a safe and sustainable future for mankind

has become extremely important. It is from these considerations that in international law a strategy for integrated management of natural resources was developed, which is called the "ecosystem approach".

Some aspects of the ecosystem approach, in particular those that indicate the dependence of human life and health and its right to a safe environment on the proper functioning of ecosystems, are enshrined in leading international legal instruments. In the 1st principle of the Declaration of the United Nations Conference on the Human Environment, adopted at the Stockholm Conference in 1972, it is noted that man has the fundamental right to adequate conditions of life, in an environment of a quality that permits a life of dignity and well-being. And in the 2nd and 6th principles it is stated that representative samples of natural ecosystems must be safeguarded for the benefit of present and future generations through careful planning or management, and negative impact on the environment must be halted in order to ensure that serious or irreversible damage is not inflicted upon ecosystems.

The Rio Declaration on Environment and Development, which was adopted at the Rio de Janeiro Earth Summit in 1992, among the main principles also outlines the human right to a healthy and productive life in harmony with nature (Principle 1) and the need for States to cooperate in a spirit of global partnership to conserve, protect and restore the health and integrity of the Earth's ecosystem (Principle 7). And adopted at that Conference Agenda 21 begins by saying that humanity is confronted with different problems including the continuing deterioration of the ecosystems on which we depend for our well-being. However, integration of environment and development concerns and greater attention to them will lead to the fulfillment of basic needs, improved living standards for all, better protected and managed ecosystems and a safer, more prosperous future (Preamble).

Such statements is enshrined in the Plan of Implementation of the World Summit on Sustainable Development (Earth Summit 2002, Johannesburg), which states that human activities are having an increasing impact on the integrity of ecosystems that provide essential resources and services for human well-being and economic activities. In this regard, to reverse the current trend in natural resource degradation as soon as possible, it is necessary to implement strategies which should include targets adopted at the national and regional levels to protect ecosystems and to achieve integrated management of land, water and living resources (Paragraph 24). And the document "The Future We Want" adopted at the United Nations Conference on Sustainable Development (Earth Summit 2012, Rio de Janeiro) declares that sustainable development can be achieved by promoting the integrated and sustainable management of natural resources and ecosystems that supports economic, social and human development while facilitating ecosystem conservation, regeneration and restoration and resilience in the face of new and emerging challenges (Paragraph 4).

The dependence of human life and health on sustainable ecosystem functioning is also well documented in the report "Ecosystems and Human Well-being: Health Synthesis", which was prepared as part of the Millennium Ecosystem Assessment (MA). This report indicates that in a fundamental sense, ecosystems are the planet's life-support systems – for the human species and all other forms of life. The needs of the human organism for food, water, clean air, shelter and relative climatic constancy are basic and unalterable. That is, ecosystems are essential to human well-being and especially to human health – defined by the World Health Organization as a state of complete physical, mental and social well-being. Those who live in materially comfortable, urban environments commonly take for granted ecosystem services to health. They assume that good health derives from prudent consumer choices and behaviours, with access to good health care services. But this ignores the role of the natural environment: of the array of ecosystems that allow people to enjoy good health, social organization, economic activity, a built environment and life itself (1.1 Introduction) [9].

The importance of conservation and restoration of ecosystems to human life and health is directly derived from WHO documents. As indicated in the document of the WHO Regional Office for Europe "Improving environment and health in the context of Health 2020 and the 2030 Agenda for Sustainable Development: outcomes of the Sixth Ministerial Conference on Environment and Health", there is a growing body of evidence crucial to understanding emerging and future challenges that shows the health of humanity and the health of the environment and the planet are intrinsically linked and that human activity is threatening to destabilize the Earth's key life-support systems. Changes to the Earth's natural systems pose a substantial threat to human health, well-being and security, and will become increasingly severe over time if no action is taken (Paragraph 4) [10].

However, the most effectively issues of international legal protection of ecosystems and implementation of the ecosystem approach are being developed under the Convention on Biological Diversity of June 5, 1992 [11], the objectives of which are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources (Article 1). The Convention defines the "ecosystem" as a dynamic complex of plant, animal and micro-organism communities and their non-living environment interacting as a functional unit (Article 2), and establishes the obligations to preserve and restore natural ecosystems. In particular, each Contracting Party shall: promote the protection of ecosystems; rehabilitate and restore degraded ecosystems; prevent the introduction of, control or eradicate those alien species which threaten ecosystems, etc. (Paragraphs "d", "f" and "h" of Article 8).

The text of the Convention doesn't specify an ecosystem approach, but there are a number of decisions of the meetings of its governing body, the Conference of the Parties (COP), which set out the framework for the ecosystem approach and its relation to a safe and healthy environment. The First Meeting of the COP, held in Nassau (Bahamas,

1994), recognized that the planet's essential goods, ecological functions and services depend on the variety and variability of ecosystems. If humanity is to have a future on this earth, biological diversity must be conserved, because its depletion causes threats to ecosystems that are vital for the sustenance of human societies in all countries (Paragraph 1 of Annex to Decision I/8).

Of particular importance to the development of the ecosystem approach was the Fifth Meeting of the COP in Nairobi (Kenya, 2000), which adopted Decision V/6 "Ecosystem Approach", that contains a description of this approach (Section A), its 12 principles (Section B) and operational guidance for their application (Section C) [12]. According to Section A, the ecosystem approach is a strategy for the integrated management of land, water and living resources that promotes conservation and sustainable use in an equitable way. An ecosystem approach is based on the application of appropriate scientific methodologies focused on levels of biological organization, which encompass the essential structure, processes, functions and interactions among organisms and environment. It recognizes that humans, with their cultural diversity, are an integral component of many ecosystems.

No less important for the development of the ecosystem approach were other meetings of the COP, in particular the Sixth (The Hague, Netherlands, 2002) and the Seventh (Kuala Lumpur, Malaysia, 2004), where the inclusion of this approach in the thematic programs of the Convention at the local, national and regional levels and the need for its implementation in national strategies and legislation of different countries were discussed.

The active development of the ecosystem approach at the international level has led to the emergence of a new area of scientific research – EcoHealth, which explores how changes in the Earth's ecosystems affect human health. According to G. Forget and J. Lebel, the ecosystem approach to human health is a new, holistic approach that flows from the metaphor of the "healthy ecosystem" – it places human beings at the center of considerations about development, while seeking to ensure the durability of the ecosystem of which they are an integral part. There can be no sustainable development unless interventions take into account both the well-being of human beings and the survival of the ecosystem. This research approach is particularly appropriate for developing countries, because it is much better able to accommodate the complexity of the systems concerned. It is not, however, an intuitive approach for researchers, and it requires a considerable philosophical adjustment. Nevertheless, this new approach is now coming into its own, especially as the impact of environmental changes on human health becomes increasingly evident [13].

The views of N. Ole Nielsen in this context are interesting too. He writes that in the course of history the human social system has become so influential and so entangled in the natural or ecological system that society can no longer act without more regard for nature. Human social systems have both local and global impacts that can impair the quality of life, predispose to disease, and even threaten life support systems. It has become essential to try to understand our world as a complex socio-ecological ecosystem and take such steps as are necessary to manage human affairs in ways that promote the health not only of people but also of the planet. Reductionist science by itself cannot deal with the complexity of this task. The ecosystem approach is one means to this end since it recognizes the interconnectedness of biotic and abiotic elements of the environment and effectively derives from a management perspective. Simply stated, managing for human health must be embedded in the wider pursuit of ecosystem health [14].

A significant contribution to the development of this issue was made by D.F. Charron, according to whom ecosystem approaches to health (or ecohealth research) formally connect ideas of environmental and social determinants of health with those of ecology and systems thinking in an action-research framework applied mostly within a context of social and economic development. Ecosystem approaches to health focus on the interactions between the ecological and socio-economic dimensions of a given situation, and their influence on human health, as well as how people use or impact ecosystems, the implications for the quality of ecosystems, the provision of ecosystem services, and sustainability. In the course of his research, the scientist forms six principles of an ecosystem approach to health (systems thinking; transdisciplinary research; participation; sustainability; gender and social equity; knowledge to action) and provides guidance on how to put these principles into practice [15].

Issues related to the study of the EcoHealth are of particular relevance to scientists in different countries today. Thus, Ziad D. Al-Ghazawi touched on the problem of the ecosystem approach to human health in two villages of the North Jordan Valley [16]. T. Asakura et al. studied this approach to health as a promising strategy in international development on the example of Japan and Laos [17]. H. Nguyen-Viet and T. Thi Tuyet Hanh identified some possibilities and problems of its application in environmental health research in Vietnam [18].

A separate direction is the study of specific diseases. Thus, R. Bazzani, L. Noronha and A. Sanchez focused their attention on the study of the use of an ecosystem approach to health for the prevention of communicable diseases [19], A. Alonso Aguirre et al. considered this issue regarding parasitic and vector-borne diseases [20], and G.N. Bratman et al. emphasized on mental diseases [21]. There are scientific publications that combine the territorial principle with specific diseases (for example, N. Arya et al. studied the expediency of implementing an ecosystem approach to public health on the lessons from two infectious disease outbreaks in Canada [22]).

The popularity of this issue led to the creation in 2010 an organization EcoHealth Alliance formed with the merger of two highly respected organizations, Wildlife Trust and the Consortium for Conservation Medicine. Building on over 45+ years of groundbreaking science, EcoHealth Alliance is a global environmental health nonprofit organization dedicated to protecting wildlife and public health from

the emergence of disease. The urgent concern for wildlife conservation and the overall health of our planet has led EcoHealth Alliance to become an environmental science and public health leader working to prevent pandemics in global hotspot regions across the globe and to promote conservation [23]. In addition, it should be noted that the EcoHealth Alliance issues the international journal "EcoHealth" which aims are to advance research, practice, and knowledge integration at the interface of ecology and health by publishing high quality research and review articles that address and profile new ideas, developments, and programs. Papers address integrated ecology and health challenges arising in public health, human and veterinary medicine, conservation and ecosystem management, rural and urban development and planning, and other fields that address the social-ecological context of health.

As for Ukraine, unfortunately, the issue of implementing an ecosystem approach to health hasn't yet become widespread in the scientific literature. At the same time, we can see positive changes in this direction, as there are some scientific articles, monographs and other publications, which advocate the implementation of a holistic (holistic) approach to health. Thus, in the monograph called "General Theory of Health and Healthcare" Yu.D. Boychuk writes that the holistic approach allows us to determine the hierarchy of levels in nature as a single holistic system, one of the elements of which is human health. In this consideration, the health problem reveals a connection with the social-ecological system as a higher-level meta-integrity. As a matter of fact, the health of an individual, ethnos, humanity are in their interconnections, on the one hand, as a condition, and on the other, as a result of the sustainable development of social-ecological system. The holistic approach makes it possible to consider all aspects of the cosmoplanetary and biopsychosociocultural nature of human. It gives an opportunity to consider health as a system-forming quality, a result of interaction of biosphere, biology and ecology of a human, his lifestyle and purposeful self-establishment on health. Characteristics of health of ethnic groups and humanity as a whole should be considered taking into account influence of factors of social evolution, history of ethnic groups and humanity. So, the holistic approach to health causes the necessity to consider the human being as a part of social-ecological system, which actively influences it and at the same time experiences the reverse action from its side. In conditions of global ecological and social-economic crisis, application of holistic approach to understanding human nature and mechanisms of human health contributes to formation of self-preservation philosophy as a worldview platform for prevention of degradation of biosphere and human [24].

More clearly and consistently, the issue of implementing an ecosystem approach in the context of ensuring the human right to a safe environment for life and health can be traced to leading environmental regulatory acts. In particular, on February 28, 2019 the Law of Ukraine "On the Basic Principles (Strategy) of the State Environmental Policy of Ukraine for the Period until 2030" was adopted [25], which at least ten subsequent years will have the status of a "leading pointer" on the way from overcoming the current environmental crisis to building a state based on the best international and European environmental standards. This Law pays considerable attention to the need to preserve and restore ecosystems. It is stated that one of the main tasks for ensuring sustainable development of natural resource potential (Goal 2) is to improve the condition of affected ecosystems, and the tasks to reduce environmental risks to minimize their impact on ecosystems, socio-economic development and public health (Goal 4) are reducing anthropogenic impacts on ecosystems and preventing the spread of invasive species and controlling their appearance in natural ecosystems.

But most importantly, in accordance with this Law, the implementation of an ecosystem approach is recognized as a necessary condition not only for stabilizing and improving the environment as a whole, but also for ensuring the human right to a safe environment. Section II, which points out the purpose, foundations, principles and tools of environmental policy, states that its goal is to achieve a good environment through the implementation an ecosystem approach to all areas of socio-economic development of the state to ensure the constitutional right of every citizen to a clean and safe environment, the introduction of balanced natural resource use, as well as the conservation and restoration of ecosystems. The consolidation of this provision is an extremely important achievement, which requires further thorough scientific development and practical implementation.

CONCLUSIONS

Thus, it can be concluded that a necessary condition for ensuring the constitutional human right to a safe (favorable, benevolent, healthy, etc.) environment for life and health and, consequently, the right to life and health, is the implementation of an ecosystem approach into national strategies and legislation of different countries, including Ukraine. The development of this approach at the international level has led to the emergence of a new area of scientific research – EcoHealth, which studies how changes in the Earth's ecosystems affect human health. In Ukraine, the issue of implementing an ecosystem approach to health is not widespread in the scientific literature yet. However, this trend is clearly visible in leading environmental regulatory act – the Law "On the Basic Principles (Strategy) of the State Environmental Policy of Ukraine for the Period until 2030".

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ORCID and contributionship:
Yevhenii P. Suietnov: 0000-0002-4094-444X [A, B, C, D, E, F]

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR
Yevhenii P. Suietnov
Yaroslav Mudryi National Law University
77 Pushkinska st., 61024, Kharkiv, Ukraine
tel.: +380 938506200
e-mail: evgeny-suetnov@ukr.net

Received: 11.04.2020
Accepted: 23.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

CANCER IN DIALYSIS PATIENTS

DOI: 10.36740/WLek202009232

Monika Wieliczko, Michał Pyrża, Jolanta Małyszko
DEPARTMENT OF NEPHROLOGY, DIALYSIS AND INTERNAL DISEASE, MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND

ABSTRACT

Cancer in dialysis patients is a common problem and is one of the most common reasons of mordibity and mortality in developed countries. An impaired renal function leads to the accumulation in the blood products of nitrogen transformation, which negatively affect organ function, especially the immune system. The Standardized Cancer Incidence is higher in patients with end-stage kidney failure than in the general population and reaches 1,18-1,42. The cancer risk is three times higher in dialysis patients over age 65 years and is more common among hemodialysis than peritoneal dialysis patients. The most common type of cancer occurring in this group of patients is urinary tract cancer which often develops on the basis of acquired cysts and in patients previously treated with cyclophosphamide. Nonetheless, patients with kidney problems are not regularly tested for these diseases and the only group that is screened for cancer are patients tested for kidney transplantation. Some problems in this topic are briefly presented in this article.

KEY WORDS: chronic kidney disease, malignancy, standardized cancer incidence, life expectancy

Wiad Lek. 2020;73(9 p. II):2079-2092

INTRODUCTION

Cancer is one of the most common reason of mordibity and mortality in developed countries, and Chronic Kidney Disease (CKD), which affects 5-15% of the population in these countries, appears to be an additional risk factor. An impaired renal function leads to the accumulation in the blood products of nitrogen transformation, which negatively affect organ function, especially the immune system and include both immunoactivation and immunosuppression disorders.

CKD also leads to the renin-angiotensin-aldosterone system (RAAS) activation [1,2] and endothelial disorders [3], what can increase the risk of cancer. The uremic toxins such as indoxyl sulfate and p-crezyl sulfate can additionally impair DNA repairing [4-6].

The abnormal immunoactivation is multifactorial, mainly affects monocytes, increased synthesis of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF) and chemokines [7-8]. This immunoactivation is additionally stimulated by the increased gut permeability, intestinal dysbiosis [8-9], exogenous factors such as potential dialysis access contamination (catheters and not native fistulas) and dialysis membranes biocompatibility [10].

The immunosuppression relates to reduced function of T and B lymphocytes, which additional affects the accelerated body aging [7, 9, 11-12].

EPIDEMIOLOGY

The risk of cancer increases with the CKD progression and, it is estimated, to be the largest in the end-stage of the disease (end-stage kidney disease – ESKD) [13-17]. We do not have standardized global statistics, data comes from different regions, in which there are additional risk factors for cancer development.

Nevetheless, all data inform us of a generally higher risk of cancer in CKD patients, especially in the end-stage of the disease, resulting in an overall standardized cancer incidence (SIR) 1.18-1.42 [19] (regional differences: Australia SIR 1,35, Denmark SIR 1,6). The cancer risk is three times higher in dialysis patients over age 65 years and is more common among hemodialysis than peritoneal dialysis patients [20-21]. Some cancer – especially urinary tract – occur in dialysis patients much more often than others (below).

The additional risk factors in dialysis patients are: acquired renal cysts [22], prolonged analgesic abuse (acetaminophen and non-aspirin nonsteroidal antiinflammatory drugs: RR – *relative risk* – 1,28 i 1,25 respectively), prolonged oral cyclophosphamide (>36g), HBV, HCV and HPV infections (Table 1).

THE MOST COMMON CANCERS IN CKD PATIENTS BEFORE DIALYSIS

Data on the incidence of cancer at particular CKD stages and their types are scarce and some studies describe conflicting data [25-32]. This is due to many factors, including the presence of nonspecific early symptoms, no clear recommendations for screening in this patient group or different age groups qualified for studies. The three largest studies on this topic from Sweden, USA and Korea [13,25-26] obtained the following results:

1. the highest risk of any cancer was found in patients with eGFR ≥105 ml/min [13, 25-26];
2. the highest risk of developing colorectal and lung cancers [13] were found in patients with eGFR ≥105 ml/min, which may, however, result from methodological errors (frequent cachexia in these patients overestimated eGFR);

Table 1. Additional risk factors of cancer in dialysis patients

Risk factor	Type of cancer
Aquired renal cysts	RCC - renal cell carcinoma
Prolonged analgesic abuse	RCC Cancinoma of renal pelvis Cancinoma of the bladder Cancinoma of the ureter
Cyclophosphamide	Cancinoma of the bladder
HBV, HCV	HCC - hepatocellular carcinoma
HPV	Carcinoma of the cervix Carcinoma of the tongue

Table 2. SIR in hemodialysis patients general and for some specific sites (Europe, USA, Australia/New Zealand, Denmark, Taiwan Hong-Kong) [50].

Cancer	SIR (about) [33]	SIR (regional differences) [50]
Kidney	4,03	2,8-12,28
Bladder	1,57	1,5-1.57
Breast	1,42	0,8-1,65
non-Hodgkin lymphoma	1,37	0,6-1,7
Lung	1,28	0,9-1,5
Liver		1,2-2
Thyroid/other endocrine		1,9-5,9
Tongue		1,2-4,21
Cervix		2,5-4
Multiple myeloma		2,5-5,2
Colorectal	1,27	0,9-1,53
Prostate	1,06	0,27-1,2

3. the cancer risk is different at different CKD stages, however, in people with reduced GFR, is the highest in the end period and appears to increase as the disease progresses;
4. it has been shown to increase non-melanoma skin cancer, urinary tract, prostate, blood cancers with eGFR decrease; the risk of breast cancer in women has not increased;
5. the risk of developing any cancer was similar in both sexes and the highest between 40 a 49 years old [13];
6. the lowest risk of cancer is difficult to determine because, in the above-mentioned studies, conflicting data were obtained (eGFR 90-104 ml/min vs 60-89 ml/min vs 45-59 ml/min respectively).

THE MOST COMMON CANCERS IN DIALYSIS PATIENTS

The risk of developing some cancers increases in the end-stage CKD compared to the general population. This risk mainly concerns urinary tract cancers (kidney, bladder), liver, thyroid, cervix, tongue as well as multiple myeloma and non-Hodgkin lymphoma [18, 22].

Other cancers usually occur by population frequency (regional differences are described) [18-22] (Table 2).

SURVIVAL OF PATIENTS WITH CANCER ON DIALYSIS

The 3-year survival of dialysis patients without cancer varies depending on the treatment method: the highest among live donor renal recipients and the lowest among hemodialysis patients (91% vs 57%) and is lower than in comparative population groups (98%). It is estimated that the survival of 50 -year- old hemodialysed man is 7.7 years and a man of a similar age in the general population – 27.7 years [33-34]. Even lower survival is recorded among dialysis patients without cancer – patients with cancer have a slightly higher mortality risk and the risk increases with the time of dialysis. One study showed the higher cancer risk in patients on dialysis for more than 3 years (9 *vs* 6,5/1000 patient-years) [35]. Despite the higher risk of death due to cancer, cardiovascular diseases are still the main cause of death in this patients group (about 50% *vs* 4%; 38 vs 7/1000 patient-years) [36-38].

THE DIAGNOSTIC AND THERAPEUTIC PROBLEMS

As mentioned above, there are no harmonized recommendations for cancer screening in CKD patients although recommendations for early detection of cancer are routinely

Table 3. Unreliable results of screening tests (NSE - neuron-specific enolase; SCC - squamous carcinoma cell antigen; CEA - carcinoembryonic antigen))

Tumor markers	Usefulness in diagnostics
Fecal occult blood testing	*High false-positive rate*
Mammography	*High false-positive rate* Higher rate of microcalcifications Higher rate of adenomas Higher rate of dense-breast tissue
Tumor markers	*High false-positive rate* (Ca-125 especially in peritoneal dialysis patients NSE SCC CEA)

used in the general population. The only recommendations in this topic were specified for patients qualified for kidney transplantation. In each case, starting diagnostics, especially in the early asymptomatic cases, it is necessary to answer the question what benefits the object gained from making the diagnosis and what treatment can be implemented considering the patient's age, general condition and comorbidities. Among the benefits we should definitely take into account the extension of life and improvement its quality. Taking into account the estimated survival of such a patient, the topic is still valid. The American Society of Nephrology (2012) recommend against routine cancer screening in dialysis patients, because of limited life expectancy [39]. The recommendations are based on population studies in which benefits of screening were only seen with an estimated minimum 10-years survival time (e.g. breast and colorectal cancers). Another problem in the CKD population, especially in dialysis patients, are unreliable screening tests results. This applies especially for tumor markers, which, in most cases, are macromolecules (3400 kD-5000 kD) ineffectively removed during hemodialysis [36-38] except AFP (alpha-fetoprotein) and PSA, whose specificity is high. The role of other antigens in cancer diagnosis is unclear in this patients group (Table 3) [40-45]. Nonetheless, it is wrong to routinely neglect or refuse cancer diagnosis in people with CKD when it is necessary to perform tests using contrast media. Each case requires a separate, precise discussion with the patient and make a joint decision.

A therapy is a separate problem. In patients with impaired renal function many adverse outcomes of surgical treatment of colorectal and lung cancers, e.g. the need for re-intubation, prolonged ventilation, higher rate tissue infection, sepsis, pneumonia and 63% higher mortality risk in dialysis patients compared to general population are demonstrated [46]. In addition to surgical problems, chemotherapy is also difficult. Many drug programs are not available to patients with impaired renal function in predialysis period or even in the initial CKD stages. The available medicines require dose adjustment appropriate to eGFR, which carries the risk of giving too little or too much drug. The influence of modern oncological therapies on the kidneys is also important. It may affect both a deterioration their function and cause a new disease in them. Patients on dialysis with cancer are treated essential as well as the general population, doses of chemotherapeutic agents need additional adjustment, taking into account their removal during dialysis procedures. However, there is still no convincing data on the oncological treatment results in this group of patients.

CONCLUSION

Cancer significantly reduce survival in the general population and somewhat in the dialysis patient population. There are more common than in the general population. In this group of patients may occur any cancer, however, urinary tract cancers have a significant advantage. There is still a discussion about the screening problem in dialysis patients. It is calculated that the expected benefit of such costly proceedings is to extend life by a maximum of 5 days and reduce the ESKD mortality rate by 0.02 percent [47-48]. Most of the studies in this topic, however, ended about 10 years ago and today this data may be unreliable, especially, mortality in the dialyzed patient group is today reduced (2001-2016 up to 29% reduction) [49]. Each case requires individual diagnosis and treatment. However, it appears that studies assessing the risk, benefits and costs of diagnostics for specific cancers are needed in large patient group. Screening procedures proposed by some researchers in the dialysis patients would only concern candidates for kidney transplantation and those whose estimated survival time is longer ten 10 year [33]. But there are no validated scoring systems to estimate the 10-year survival of dialysis patients (calculators for the general population are available online) which would greatly facilitate diagnostic and therapeutic decision. Although the data from years ago showed that a 20-year-old patient with kidney cancer and the estimated survival time of 25 years after cancer treatment will extend the life of about 1.6 years but a 58-year-old patient by only 4-5 days, there is no current data taking into account today's reality [50]. Screening for urinary tract cancer rather should be done regularly especially as the number of acquired kidney cysts increases as the time of dialysis increases and the cysts are the risk factor for kidney cancer. We also believe that screening in

the remaining groups of patients with reduced glomerular filtration in a predialysis period should be conducted as in the general population.

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ORCID and contributionship
Monika Wieliczko – 0000-0002-6172-0218 [A, B, D]
Michał Pyrża – 0000-0002-0897-4235 [E]
Jolanta Małyszko – 0000-0001-8701-8171 [F]

Conflict of interest
Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Monika Wieliczko
Department of Nephrology, Dialysis and Internal Disease
Medical University of Warsaw,
Żwirki i Wigury, 61, 02-091, Warszawa, Poland
e-mail: monfeb@wp.pl

Received: 19.06.2020
Accepted: 09.09.2020

REVIEW ARTICLE

THE RELEVANCE OF THE DEVELOPMENT AND IMPLEMENTATION OF QUALITY SYSTEM IN CLINICAL DIAGNOSTIC LABORATORIES

DOI: 10.36740/WLek202009233

Rymma F. Yeromenko[1], Maryna O. Ostapets[1], Olexiy B. Datsenko[2], Olga M. Lytvynova[1], Hanna L. Lytvynenko[1]
[1] NATIONAL PHARMACEUTICAL UNIVERSITY, KHARKIV, UKRAINE
[2] MUNICIPAL NON-PROFIT ENTERPRISE "CITY CLINICAL HOSPITAL No 2 NAMED AFTER PROF. A. A. SHALIMOV" OF THE KHARKOV CITY COUNCIL, KHARKIV, UKRAINE

ABSTRACT

The aim: to analyze the implementation of international standards ISO series, which ensures the creation of uniformity of measurements, the ability to use the results of laboratory studies to ensure their reliability and reproducibility.

Materials and methods: the samples were taken from the ISO documents, the Regulation and the Quality Decree of clinical diagnostic laboratory (2017) that is the object of the research activities of the clinical diagnostic laboratory "City clinical hospital № 2 named after Prof. A. A. Shalimov".

Conclusions: The introduction of international standards of the ISO series into the domestic laboratory practice ensures the creation of a single medical space, the uniformity of measurements, the possibility of using the results of laboratory studies with an increase in their reliability and reproducibility.

KEY WORDS: laboratory research, quality system, state standards

Wiad Lek. 2020;73(9 p. II):2084-2088

INTRODUCTION

One of the most important components of the Ukrainian health care system of Ukraine is clinical laboratory diagnostics, which is of national importance for the preservation and improvement of public health [7, 10]. Modern laboratory diagnostics provides medical and diagnostic assistance to patients in assessing the state of health, diagnosis of diseases, monitoring the results of treatment, further prognosis of the disease and quality of life [2].

Laboratory research is one of the most important segments in healthcare. Today, one of the main tasks of the clinical laboratory diagnostics service is to improve the quality of laboratory tests, which can be implemented by using modern technologies and equipment, improving laboratory methods and procedures, and changing outdated principles and stereotypes of the quality management system [3]. From 30 to 45 % of cases of diseases cannot be diagnosed correctly without objective examination data, among which the results of clinical laboratory studies are 60-80 % [5].

In laboratory medicine in developed countries, the error range is 0.1-3.0 % of the total results of laboratory studies (errors at all stages of research). Therefore, in connection with the solution of this problem, it is urgent to develop and implement the requirements of ISO standards for medical laboratory practice. This will reduce the level of errors in laboratory research. Up to modern quality standards include: ISO 15393, ISO 15194, ISO 15195, ISO 17511, ISO 18153, ISO 17025, ISO 15189, ISO 10012, which establish requirements for the creation of reference systems for medical laboratory research [7, 9, 10]. Standards are the main condition for the suitability of the results of medical laboratory tests, they provide comparability of results in time and space [1, 6]. It is also important to analyze the international experience of accreditation of clinical diagnostic laboratories, the development of stages of implementation of the requirements of DSTU ISO 10012:2005, the basic procedures of the quality system of the laboratory, in particular the Regulations of the laboratory, Quality Decree and laboratory Passport.

THE AIM

To study the feasibility and importance of the implementation of the state standard ISO 10012:2005 in the field of clinical laboratory diagnostics.

MATERIALS AND METHODS

The object of the research is the activity of the clinical diagnostic laboratory of the municipal non-profit enterprise (KNP) "City clinical hospital № 2 named after Prof. A. A. Shalimov" of the Kharkiv city Council. The material was ISO documents, the Regulations on clinical diagnostic laboratory (2017).) [1, 4, 7, 9, 8], Quality Decree of clinical diagnostic laboratory. The methods stated in the certificate (according to the appendix) are confirmed in accordance with the requirements of DSTU ISO 10012: 2005.

Measuring equipment (a hematology analyzer, photoelectric concentration colorimeter KFK-2, microscope Biolan R-11, immunoassay analyzer STAT-FAX 4700, chemistry analyzer RT-9200, AGKM-01, Exan-G, coagulometer K-3302 OPTIC photometer Laura Smart urine analyzer, gas chromatograph Agilent 7890 B, mass detector Agilent 5977 B, pipette dispenser P-1, urometer) and accessories used according to the normative documents, which are presented in the laboratory Passport.

REVIEW AND DISCUSSION

The main function of the clinical diagnostic laboratory of KNP " City clinical hospital № 2 named after Prof. O. Shalimov "according to the" Regulations on clinical diagnostic laboratory "(2017) is a timely and qualitative examination of patients. The definition of indicators in biological materials is carried out using the following equipment: a hematology analyzer, photoelectric concentration colorimeter KFK-2, microscope Biolan R-11, immunoassay analyzer STAT-FAX 4700, chemistry analyzer RT-9200, AGKM-01 and Exan-G (for glucose definition in blood serum), coagulometer K-3302 OPTIC photometer Laura Smart urine analyzer, gas chromatograph Agilent 7890 B, mass detector Agilent 5977 B, the pipette dispenser P-1, urometr. The analytical activity of the laboratory includes: the analysis of forms and methods of the analytical activity; the introduction of advanced methods and the directions of laboratory service, providing the laboratory with the information about new research methods, the equipment and auxiliary materials, normative documents; the improvement of the system of internal and external quality control of laboratory studies.

DSTU ISO 10012: 2005" Measurement control systems. The Requirements for measurement processes and measuring equipment" was developed and implemented in clinical and diagnostic laboratory of KNP " City clinical hospital № 2 named after Prof. O. O. Shalimov "of the Kharkiv city Council, as evidenced by the Certificate № 01-0009/2017 from 21.02.2017. The Laboratory conducts laboratory studies: hematological, general clinical, biochemical, serological, cytological, toxicological and microbiological in accordance with the profile of the laboratory and in the volume that corresponds to the scale and needs of the medical institution. Quality requirements are set once every three years, the implementation of which is certified by the procedure of analysis by senior management.

The scope of measurement objects and processes of the measurement system, which is covered by the Certificate, includes the research:

- blood serum – the determination of triglycerides, high-density lipoproteins and cholesterol by enzymatic-photometric method; uric acid by phosphoric-tungsten reaction; potassium and sodium by ion selective method; cholesterol and low-density lipoproteins; triglycerides with the calculation of very low-density lipoproteins; cholesterol and low-density lipoproteins with the calculation of atherogenicity coefficient; surface antigen hepatitis B express test; antibodies to HCV express test; antibodies to troponin, myoglobin, express test of creatinine phosphokinase-MB; antibodies to Helicobacter pylori by express test; of alanine aminotransferase and aspartate aminotransferase by kinetic method; bilirubin for diazoreaction in the presence of the accelerator; the activity of α-amylase by Karavey alloplastic method of resistant starch substrate; activity of alkaline phosphatase by kinetic method; rheumatoid factor by latex test; C-reactive protein by latex test; total protein by biuret reaction; protein fractions by turbidimetric method,by method of gel electrophoresis; creatinine by Jaffe colour reaction; urea by the colour reaction with diacetylmonooxime; thymol samples; glucose by glucoseoxidase method; glucose for AGKM-01 and Exan-G;

-blood venous- morphological study of blood cells with differential counts and morphology of red blood cells using Papenheim staining; counting the number of erythrocytes and leukocytes by impedance method using a hematology analyzer; hemoglobin by photometrical method using a hematology analyzer; carboxyhemoglobin by Fervust-Minex method ; the clotting time by Lee-White; blood group system AB0 with the help of test reagents anti A, anti B; RH factor with a test reagent anti-D; the method of dehydration of fructose phosphoric acid; tension immunity to tetanus by ELISA; study on lupus erythematosus cells by Zinkham method ; determination of erythrocyte sedimentation rate by Panchenkov micro-method;

- capillary blood –the platelet counts by impedance method and using a hematological analyzer; reticulocytes after staining them brilliant blue, Azur I, Azur II; determining the time of coagulation by Moravitz; duration of bleeding by Duke; blood test for malaria by thick drops and smears;

-plasma – determination of fibrinogen by Klaus; partial thromboplastin time with adding calcium chloride; degree of coagulation by Fuene-Ita method; plasma tolerance to heparin; factors of prothrombin complex; prothrombin time with calculation of international normalized ratio;

-urine – determination of physico-chemical properties of urine; pH using the indicator bromthymol blue; specific weight using a urometer; the quality of the sample with 20% sulfosalicylic acid in a protein; the protein with the turbidity formed by the addition of 3 % sulfosalicylic acid; the qualitative reaction for the presence of urine glucose using test strips "Glucotest"; the number of glucose by glucose oxidase method; microscopic examination of urine sediment in the native preparation; ketone bodies using the express method, quality test on bilirubin by reaction with iodine solution, amount of shaped elements in 1 ml of urine by Nechiporenko method; red blood cells and white blood cells using test strips;

- cerebrospinal fluid – conducting Jonne-Apelt reaction; counting cytosis using a counter; microscopic examination of drugs stained by Romanovsky method;
- duodenal content – determination of physical properties of bile; microscopic examination of bile in native preparation;
- gastric contents – determination of gastric acidity by titration; microscopic examination of gastric juice;

- fecal – microscopic fecal examination; for occult blood, benzidine test; detection of the simpliest intestines in feces by native smear method with Lugol's iodine; smear on cryptospora stained by Romanovsky; identification of larvae in feces by Berman method and by the method of enrichment;
- liquids of serous cavities-a microbiological study on the detection and identification of infectious agents; microscopic examination of the sediment of exudates and transudates; determination of physical properties of exudates and transudates; specific gravity using a urometer; protein 3% sulfosalicylic acid;
- sputum – microbiological methods of sputum examination;
- preanal scraping-detection of helminth larvae in preanalocular scrapings using a sticky strip.

Due to the internal and external quality control quantitative indicators of the clinical and diagnostic laboratory of the KNP "City clinical hospital № 2 named after Prof. A. A. Shalimov" of the Kharkiv city Council according to the results of the statistical report for 2018 are 504 731 laboratory studies, including: general clinical – 111 777, hematological – 143 373, cytological – 108, toxicological – 2 135, biochemical – 218 741, bacteriological – 16 397, immunological – 11 200.

Thus, the clinical and diagnostic laboratory has established, implemented and maintains a quality management system according to ISO 10012:2005 according to the scope of its activities, as well as ensures its further continuous improvement in order to improve the effectiveness and efficiency of measurement processes.

CONCLUSIONS

1. The introduction of international standards of the ISO series into the domestic laboratory practice ensures the creation of a single medical space, the uniformity of measurements, the possibility of using the results of laboratory studies with an increase in their reliability and reproducibility.
2. Development and implementation of the quality system according to the requirements of the standard DSTU ISO 10012:2005 "Measurement control system. Requirements to measurement processes and measuring equipment" in the activity of clinical and diagnostic laboratory of KNP "City clinical hospital № 2 named after Prof. A. A. Shalimov" of the Kharkiv city Council provides high quality of clinical and laboratory research.
3. The quality system of clinical diagnostic laboratory of KNP "City clinical hospital № 2 named after Prof. A. A. Shalimov" of Kharkiv city Council meets the requirements of ISO standards and is the key to protecting citizens of Ukraine from the consequences of inaccurate measurement results.

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ORCID and contributionship:

Rymma F. Yeromenko: 0000-0001-8868-8935 [A,F]
Maryna O. Ostapets: 0000-0002-6900-5833 [D]
Olga M. Lytvynova: 0000-0002-0996-2500 [B]
Hanna L. Lytvynenko: 0000-0001-5727-5361 [B]
Olexiy B. Datsenko: 0000-0002-7428-8217 [E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Hanna L. Lytvynenko
National University of pharmacy
12 Kulikov str., 61002 Kharkiv, Ukraine
tel: +380679998513
e-mail: litvinenko.79anna@gmail.com

Received: 23.09.2019
Accepted: 03.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

REVIEW ARTICLE

THE ROLE OF PET/CT WITH 11C-METHIONINE IN CONTEMPORARY NUCLEAR MEDICINE

DOI: 10.36740/WLek202009234

Maciej Kołodziej, Barbara Bober, Marek Saracyn, Grzegorz Kamiński
DEPARTMENT OF ENDOCRINOLOGY AND ISOTOPE THERAPY, MILITARY INSTITUTE OF MEDICINE, WARSAW, POLAND

ABSTRACT

Positron emission tomography (PET/CT) is a non-invasive molecular imaging technique using isotopes with a short half-life usually in combination with chemical compounds. The most commonly used PET/CT tracer is 2-fluoro-2-deoxy-D-glucose labeled with fluorine (18-FDG). It is used mainly in oncological diagnostics as well as myocardial viability, epilepsy and inflammatory diagnostics. The tracer less commonly used in PET/CT could be carbon-labeled methionine (11C-MET). It is mainly used in the diagnosis of focal lesions in the central nervous system. There are also reports of the use of this tracer in diagnostics of the primary, secondary and tertiary hyperparathyroidism as well as multiple myeloma. This tracer may also be used in the diagnosis of lymphoproliferative diseases and solid tumors, although there is no clear evidence of its advantage over 18-FDG.

Conclusion: Significant difficulties in the production and transport of this tracer and lack of reimbursement of this type of procedure in Poland limits the use of this tracer for scientific research.

KEY WORDS: PET/CT, methionine, hyperparathyroidism, multiple myeloma, brain tumor

Wiad Lek. 2020;73(9 p. II):2087-2102

INTRODUCTION

Positron emission tomography (PET/CT) is a non-invasive diagnostic technique that uses short-lived, beta plus isotopes, which, thanks to the combination of substances naturally occurring in the human body, allows to track selected metabolic pathways and cell functions quite precisely. The most common tracer used in PET/CT diagnostics in Poland and other countries is fluoride-18 deoxyglucose (18-FDG), which is widely used in oncology, cardiological, neurological and inflammatory diagnostics [1]. Among the other tracers, carbon-11 labeled methionine (11C-MET) deserves attention. Methionine is one of the exogenous amino acids, isolated for the first time in 1921 by John Howard Mueller, mainly used for the synthesis of proteins, and as a cofactor for the transfer of carbon residues, and for energy production by incorporating into the citric acid cycle [2, 3]. To obtain a tracer useful for PET/CT one of the stable carbon atoms in a methionine molecule is replaced by an 11-C isotope atom with a half-life of 20.4min and a maximum radiation energy of 0.96MeV in the cyclotron as a result of the reaction between nitrogen and protons [4]. 11C-MET is a marker whose transport over considerable distances is technically impossible due to its short half-life. It is usually used in departments equipped with a cyclotron in which this tracer is produced. 11C-MET is most widely used in neurooncological diagnostics, as well as in the hematology and endocrinology [5, 6]. The short half-life means that the exposure to ionizing radiation of a patient undergoing a diagnostic procedure using 11C-MET is lower than in the case of much more frequently performed procedures with 18-FDG, and the critical organs for this marker are the pancreas and liver, in which the physiological uptake of 11C-MET is highest due to the anabolic functions of these organs, as well as the bladder due to urinary marker excretion [7, 8]. The examination is performed approximately 10-20 minutes after intravenous administration of the tracer, and no serious adverse effects associated with the administration of 11C-MET have been reported in the available literature [6, 9].

PET/CT WITH 11C-METHIONINE IN NEUROONCOLOGY

The widest application of PET/CT with 11C-MET is in the diagnosis of brain tumors, first of all the most common gliomas, which are characterized by high mortality [10, 11]. The big advantage is the very low tracer uptake in healthy brain tissue. The mechanism of 11C-MET accumulation in pathological lesions is not fully expleined. The most likely explanation for this phenomenon is damage to the natural blood-brain barrier resulting in passive diffusion of the tracer into the tumor tissue with the additional occurrence of active transport to the cancer cell caused by increased proliferation. Thanks to these two mechanisms, a good tumor/background ratio can be obtained [6]. The intensity of 11C-MET uptake in a tumor is associated with its grading and malignancy – in tumors with higher proliferative potential and higher histological malignancy usually higher tracer accumulation is observed [6]. This makes 11C-MET often used in the diagnosis of the effectiveness of surgical treatment and to confirm or exclude recurrence after chemotherapy or radiation therapy. In these situations, imaging with radiological techniques is character-

ized by low specificity (24-44,4%) and may give ambiguous, false positive results in connection with post-treatment necrotic lesions, fibrosis, edema zones or scar lesions [10, 12-14]. In morphological studies, these changes may give an image similar to proliferative lesions. However, they do not show 11C-MET uptake in PET/CT, which allows for fairly accurate differential diagnosis of post-therapeutic changes and recurrence. The sensitivity and specificity of this type of examinations are estimated at over 90% [10]. In pre-therapeutic diagnostics, PET/CT with 11C-MET can be used to plan radiation therapy and defining tumor boundaries quite accurately, which helps reduce irradiation of healthy tissue, and by narrowing the irradiation field, allows to intensify the absorbed dose in the tumor. PET/CT with 11C-MET may also indicate the potentially most favorable site for biopsy by selecting the area with the highest tracer accumulation. The change in the intensity of 11C-MET accumulation in the tumor in subsequent, repeated studies may be an indicator of a change in the histological grade of the tumor and indicate its differentiation. The clinical manifestations of tumors with high, intensive 11C-MET accumulation seen in PET/CT are usually more rapid, affecting shorter patient survival and mortality. The intensity of 11C-MET accumulation in central nervous system tumors is not affected by corticosteroid treatment for anti-edema purposes [6].

Benign brain lesions, such as meningiomas, may also be characterized by 11C-MET uptake in PET/CT. A comparative study in 22 patients found a higher rate of accumulation of radiolabeled methionine in meningioma lesions compared to the uptake observed in PET/CT with 18-FDG, with better quality images and a better tumor/background ratio, which is caused by a natural, physiological accumulation of 18-FDG in normal brain tissue [15].

Low availability of the tracer in departments that do not have a cyclotron for its production remains the main limitation of the PET/CT with 11C-MET. Due to the physical properties of the 11C isotope and the energy of the positron emitted from its nucleus, the spatial resolution of the method is estimated at about 5mm, which may also be a certain limitation of the diagnostic capabilities of PET/CT with methionine labeled with this isotope. Currently in Poland, the 11C-MET tracer is not reimbursed by the national public health system in any of the indications, which is significantly limits its use in clinical practice.

A different issue could be pituitary gland tumors. Even in normal, unchanged pituitary gland, physiological accumulation of 11C-MET is observed [16]. The mechanism of 11C-MET uptake in hormonally active adenomas is associated with increased cellular proliferation and with the fact that methionine is one of the substrates needed for hormone synthesis by pituitary cells. In the literature, there is evidence of the usefulness of the PET/CT with 11C-MET in the preoperative diagnosis of pituitary corticotropic adenomas, as well as in the diagnosis of recurrence of ACTH-dependent Cushing's syndrome after surgery [17]. This technique is also useful in the diagnosis of other hormonally active pituitary adenomas, especially in the case of ambiguous or doubtful results obtained in magnetic resonance imaging [18, 19].

THE USE OF PET/CT WITH 11C-METHIONINE IN HEMATOLOGICAL AND ONCOLOGICAL DIAGNOSTICS

Among the various clinical attempts to use the PET/CT 11C-MET study for oncological diagnosis in recent years, the most promising reports show the role of this study in monitoring multiple myeloma. A commonly used marker in myeloma imaging is 18-FDG, whose effectiveness in initial diagnostics and in assessing the effectiveness of treatment has been confirmed by many studies [20, 21]. The limitation of this method is often low glucose metabolism and high heterogeneity of pathological lesions. Initial good experiments using 11C-MET PET/CT in the diagnosis of myeloma and the results of in vivo and in vitro studies on CD138 + cells prompted several teams to further research [22, 23]. A two-center study of 78 patients demonstrated the superiority of PET/CT with 11C-MET over 18-FDG in the detection of myeloid and extramedullary lesions in multiple myeloma, what according to the authors could complete replace glucose tracer by amino acid one in the future [24]. The likely mechanism of 11C-MET uptake in myeloma foci is associated with the incorporation of methionine into immunoglobulin synthesized in lesions, resulting in 11C-MET uptake intensity in a simple way correlating with disease activity, the degree of bone marrow involvement, ß2 macroglobulin concentration and the concentration of free light chains (FLC), which are important prognostic factors in the course of multiple myeloma [24,25]. In another study involving 19 patients with multiple myeloma, higher sensitivity of PET/CT with 11C-MET over PET/CT with 11C-choline in detection of pathological changes was found [26].

Among the other hematological diseases, use of the PET/CT with 11C-MET in assessment of the early response to methotrexate-based chemotherapy on primary central nervous lymphoma (PCNSL), which has a poor prognosis, deserves mention. A study assessing 26 patients who underwent PET/CT 11C-MET after 4 cycles of high-dose chemotherapy (interim-PET) found that high tracer uptake in interim-PET was associated with a statistically significant reduction in progression-free survival (PFS) and was a bad prognostic factor in the PCNLS [27].

In the literature you can also find reports of individual cases of patients with various types of lymphoproliferative hyperplasia, in whom the PET/CT examination with 11C-MET allowed better assessment of the disease staging, compared to the standard PET/CT examination with 18-FDG, but currently it is not a standard procedure for lymphoma diagnosis [28].

In the 1990s and at the beginning of the 21st century studies assessing the usefulness of PET/CT imaging with 11C-MET in the diagnosis of solid tumors, especially mammary gland cancer and lung cancer were conducted. However, this work did not bring the expected result. The advantage of diagnostics using 11C-MET over 18-FDG has not been proved, with a much more favorable half-life time of 18-FDG (109min), which allows transporting the tracer even over a considerable distance, which makes PET centers independent of having their own cyclotron [29, 30].

Of the ongoing clinical trials, the large study of 650 patients in St. Jude Children's Research Hospital in Memphis (USA), which aims to assess 11C-MET uptake in all newly diagnosed nervous system tumors and lymphomas and sarcomas of soft tissues and bones, as well as other cancers is worth mentioning. The planned ending of the study is expected in 2023.

THE USE OF PET/CT WITH 11C-METHIONINE IN THE DIAGNOSIS OF HYPERPARATHYROIDISM

The main method of treating hyperparathyroidism, regardless of its cause, is the surgical removal of the autonomic parathyroid gland. This is the only effective method to cure the disease [31, 32]. Traditionally, in the surgical treatment of hyperparathyroidism, to visualize all four parathyroid glands bilateral neck exploration was used, which is a large-scale procedure [33]. Nowadays minimally invasive parathyroidectomy (MIP) in surgical treatment is performed more often thanks to improvement in imaging diagnostics [34]. However, precise preoperative localization of the autonomic parathyroid is necessary for this type of surgery.

For preoperative localization, the double-tracer subtraction scintigraphy of parathyroid glands using 99mTc and 99mTc-MIBI and ultrasound remains the gold standard. Scintigraphy is a sensitive method of detection of a single adenoma, unfortunately its value decreases in the presence of multiple lesions or concomitant focal lesions in the thyroid gland [35]. Even more than 30% of parathyroid adenomas found in primary hyperparathyroidism do not accumulate the 99mTc-MIBI tracer [36]. In secondary and tertiary hyperparathyroidism, the sensitivity of scintigraphy using 99mTc and 99mTc-MIBI is lower than in the case of primary changes and is assessed 36.6-62.8%, which is a significant diagnostic problem [37, 38]. The parathyroid glands may be ectopic, located in the mediastinum, being other diagnostic problem. 11C-MET is a substrate for the production of the parathyroid hormone precursor and is therefore actively accumulated in parathyroid gland cells [39]. Studies of the efficacy of the PET/CT test with 11C-MET in the diagnosis of hyperparathyroidism present in the literature were conducted on small heterogeneous groups of patients, presenting various, divergent (from 44 to 84%) results of sensitivity and specificity of this examination. However, all the authors claim that this study may complement the pre-operative localization diagnostics of patients with primary hyperparathyroidism, in whom standard double-tracer subtraction scintigraphy and ultrasound do not provide a clear result allowing for effective MIP surgery [40, 41]. In addition, some authors show evidence of the superiority of PET/CT diagnostics with 11C-MET over scintigraphy in patients who have previously undergone surgical treatment and who have recurrent hyperparathyroidism [42, 43]. Due to the larger scope of the PET/CT scan compared to the scintigraphy, it may also have an advantage in patients with ectopic lesions and multiple lesions, which are more common in secondary and tertiary hyperparathyroidism (e.g. in patients undergoing renal replacement therapy) [43, 44]. As for the safety of these studies, the absorbed dose that the patient receives from the isotope during the PET/CT with 11C-MET made to assess the location of the parathyroid glands is more than four times lower than the dose absorbed during standard scintigraphy [45].

CONCLUSIONS

The PET/CT examination with 11C-MET has its well-established position in the diagnosis of brain proliferative diseases, which is confirmed by rich literature. It is also becoming increasingly important in monitoring the treatment of multiple myeloma. It is also useful in the diagnosis of primary, secondary and tertiary hyperparathyroidism.

The limitation of the method is primarily the lack of tracer in hospitals without their own cyclotron. In Poland, the tracer is not reimbursed by the National Health Fund (pol. Narodowy Fundusz Zdrowia) and its use is limited to scientific research.

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ORCID and contributionship

Maciej Kołodziej – 0000-0003-1943-264X [A,B,D]
Barbara Bober – 0000-0002-1880-1389 [A,E]
Marek Saracyn – 0000-0002-5800-0500 [A,E-F]
Grzegorz Kamiński – 0000-0002-2357-0634 [F]

Conflict of interest

Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Department of Endocrinology and Isotope Therapy,
Military Institute of Medicine,
Szaserów 128, 04-141, Warszawa, Poland
e-mail: mkolodziej@wim.mil.pl

Received: 25.06.2020
Accepted: 15.09.2020

REVIEW ARTICLE

LEGAL REGULATION OF THE PROPER NATURAL ENVIRONMENTAL CONDITIONS AS AN INTEGRAL ENVIRONMENTAL HEALTH COMPONENT

DOI: 10.36740/WLek202009235

Oleksii S. Soloviov[1], Maryna V. Trotska[2], Bogdan V. Derevyanko[3]
[1]NATIONAL SECURITY AND DEFENSE COUNCIL OF UKRAINE, KYIV, UKRAINE
[2]DEPARTMENT OF CONSTITUTIONAL, ADMINISTRATIVE, ENVIRONMENTAL AND LABOUR LAW, POLTAVA LAW INSTITUTE, POLTAVA, UKRAINE
[3]DONETSK LAW INSTITUTE OF THE MINISTRY OF INTERNAL AFFAIRS OF UKRAINE, UKRAINE

ABSTRACT

The aim: To investigate the legal basis for natural environmental protection as an integral environmental health component.

Materials and methods: In this work we study statutory regulations and scientific positions of scholars regarding above-mentioned issue. The study analyses generalized information from scientific journals by means of scientific methods from a medical and legal perspectives. This article is based on dialectical, comparative, analytic, synthetic and comprehensive research methods. Applying systematic approach, as well as analysis and synthesis, we investigated legal regulation for proper condition of natural environment as an integral environmental health component

Conclusions: Maintaining proper condition of natural environment is one of the main tasks of each individual at many levels - international, national and personal. This would allow to accommodate proper human activity. It is implemented through a comprehensive approach to recognize the value of natural environment in the development and improvement of human health. In said processes it is important to define the indicators that allow us to monitor the state of the natural environment and its changes in both positive and negative directions. Defining them at the regulatory level allows for laying down benchmarks that help in ranking those changes in the study

KEY WORDS: health, environmental health, environmental quality indicators, environmentally responsible behaviour indicators, indicators of consumption of environmental services

Wiad Lek. 2020;73(9 p. II):2091-2098

INTRODUCTION

The vision of an ecologically sustainable society includes protection of human health, preservation of biodiversity, conservation of valuable natural and historical settings, an ecologically sustainable supply and efficient use of energy and other natural resources. In order to determine how well basic environmental quality objectives and more precise objectives are being met it is necessary to continuously monitor and evaluate the state of the environment [1, p. 9]. The environment plays a crucial role in people's physical, mental and social well-being. Despite significant improvements, major differences in environmental quality and human health remain between and within European countries. The complex relationships between environmental factors and human health, taking into account multiple pathways and interactions, should be seen in a broader spatial, socio-economic and cultural context [2, p. 91].

Human health is a value given with the birth. Its condition depends on various factors that directly or indirectly affect it, such as the health of his parents and the circumstances it was formed under, namely the environment in general and the natural environment in particular. It reflects impacts both positively and negatively. Its extension is connected to a person's awareness of causes and effects from their actions or inaction, the state of the environment that affects them and leads to the corresponding consequences. The higher the level of awareness, the better human health.

According to the Constitution of the World Health Organization health is «a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity» [3]. The environment is important to human health. However, only in recent years science and technology have provided us with ways to measure the correlation between a healthy environment and a healthy body. The natural environment in which we spend our days and the national and international community in which environmental protections must be negotiated provide both a local and a global perspective by which to consider environmental health [4].

Therefore, environmental health often associated with environmental impact assessment [5]. Environmental health addresses all the physical, chemical, and biological factors external to a person and all the related factors impacting behaviours. It encompasses the assessment and control of those environmental factors that can potentially affect health. It is targeted towards preventing disease and creating health-sup-

portive environments. This definition excludes behaviour not related to environment as well as behaviour related to the social and cultural environment, and genetics [6]. Those aspects of human health and disease are determined by factors in the environment. It also refers to the theory and practice of assessing and controlling factors in the environment that can potentially affect health. Environmental health includes both the direct pathological effects of chemicals, radiation and some biological agents, and the effects (often indirect) on health and well-being of the broad physical, psychological, social and aesthetic environment, which includes housing, urban development, land use and transport [7]. Environmental health is the science and practice of preventing human injury and illness and promoting well-being by – identifying and evaluating environmental sources and hazardous agents and – limiting exposures to hazardous physical, chemical, and biological agents in air, water, soil, food, and other environmental media or settings that may adversely affect human health [8]. Environmental health indicators, based on proven cause-effect relationships, serve as important tools for identifying potential risks to human health and for policy making [9]. As drawn from vocabulary sources, environmental health indicators – are indicators that describe the link between environment and health by measuring the health effect due to exposure to one or several environmental hazards [10, p. 29].

Thus, analysing these concepts we can conclude that human health is directly or indirectly affected by a variety of factors that have a certain nature of origin, although their direct effect occurs within the natural environment.. Various authors [11-17] carried out study on the influence of individual aspects on human health. Those works reflected relevant provisions of such influence. The natural environment, commonly referred to simply as the environment, is a term that encompasses all living and non-living things occurring naturally on Earth or some region thereof [18]. The natural environment is the thin layer of life and life support called the biosphere, that contains the earth's air, soil, water, and living organisms [19].

All other components of environmental health depend on its proper status, so studying the requirements that provide certain conditions for maintaining and improving human health is essential. According to p. 25 of Preamble to Decision No 1386/2013/EU of the European Parliament and of the Council of 20 November 2013 on a General Union Environment Action Programme to 2020 'Living well, within the limits of our planet' [20]: environmental problems and impacts continue to pose significant risks for human health and well-being, whereas measures to improve the state of the environment can be beneficial.

THE AIM

To investigate the legal basis for natural environmental protection as an integral environmental health component.

MATERIALS AND METHODS

In this work we study statutory regulations and scientific positions of scholars regarding above-mentioned issue. The study analyses generalized information from scientific journals by means of scientific methods from a medical and legal perspectives. This article is based on dialectical, comparative, analytic, synthetic and comprehensive research methods. Applying systematic approach, as well as analysis and synthesis, we investigated legal regulation for proper condition of natural environment as an integral environmental health component

REVIEW AND DISCUSSION

The connection between protecting the natural environment and safeguarding human health has been recognized for some time. The effect of various environmental exposures, such as toxic chemicals, air pollution, and biological agents on the human body, is commonly perceived as the central problem in environmental health. However, maintaining a healthy environment extends beyond controlling these hazards [19].

Therefore, by tracking and analysing such interdependency, one can understand the cause and effect relationships between negative factors that cause damage, first and foremost, to the natural environment, which is a human habitat, and affects human health accordingly, through its deterioration, which can manifest in diseases of various severity. The environment directly affects health status and plays a major role in quality of life, years of healthy life lived, and health disparities [21]. The degradation of the environment, through air pollution, noise, chemicals, poor quality water and loss of natural areas, combined with lifestyle changes, may be contributing to substantial increases in rates of obesity, diabetes, diseases of the cardiovascular and nervous systems and cancer – all of which are major public health problems for Europe's population [22].

An even more direct connection between the environment and health is the potential enhancement of our physical, mental, and social well-being through our daily exposure to the natural environment [19]. The contact with the natural the world – with animals, plants, landscapes and desert – can offer health benefits [23, p. 238]. Ergo, improvement of the natural environment conditions has a positive impact on human health. The natural environment, broadly conceived, can also enhance health, for example, many pharmaceuticals are derived from plants and animals providing a compelling argument for preserving biodiversity. In addition, contact with the natural world may be directly beneficial to health [24].

Environmental quality, air quality, soil quality, and water quality, are defined as measures of the condition or state of each relative to the requirements of one or more biotic species and/or to any human need or purpose [25]. Environmental quality is a state of environmental conditions in environmental media, expressed in terms of indicators or indices related to environmental quality standards [26, p. 30].

The quality of natural environment is determined by certain indicators, based on which one can speak about good or, conversely, bad quality of natural environment for human life and health. Environmental quality criterion –

criteria followed in establishing standards for exposure to pollutants and noise, in respect of pesticides, detergents, composition of effluents, discharge of trade wastes, etc. [27]. As noted at the theoretical level [28, p. 11] in the analysis of relevant sources [29] the most important natural environment indicators relevant to quality of life would inform about quality of several environmental media (soil, water, air), on people access to environmental services and amenities and environmentally responsible behaviour as well. In addition, the criteria that characterize the state of the natural environment, which in one way or another affect human health, are defined as: environmental quality indicators, environmentally responsible behaviour indicators and indicators of consumption of environmental services [28, p. 17]. These groups are related because responsible behaviour has a positive impact on environmental quality, which leads to higher consumption of services provided by the environment [30].

Let's analyse these components in the context of the concept in hand. Firstly, we should pay attention to the environmental quality indicators. Environmental quality indicators are used to assess the environment's capacity for supporting human and ecological health [31, p. 173]. As noted at the theoretical level, the environmental quality indicators encompass some environmental mediums (such as soil, water, air and waste) [30]. Among outlined criteria we should pay a particular attention to those related to the corresponding condition of natural objects, along with other factors, can both positively and negatively affect human health. These include indicators that characterize such environmental components as land, water and air. Undoubtedly, each of these natural resources, and namely the compliance of their condition with the requirements of environmental safety, is important both in the development and maintenance of human health. Water quality and air pollution levels are still problematic in many parts of Europe, and Union citizens continue to be exposed to hazardous substances, potentially compromising their health and well-being. Unsustainable land use is consuming fertile soils, and soil degradation continues, resulting in impacts on global food security and the achievement of biodiversity targets (p. 6 Annex The 7th Environment Action Programme to 2020 'Living well, within the limits of our planet' [20]).

When examining the nature of these indicators, it would also be appropriate to pay attention to environmental quality standards, defined in sources as limit for environmental disturbances, from ambient concentration of pollutants and wastes, that determines the maximum allowable degradation of environmental media [26, p. 30]. According to clause 6, part 1, Article 3 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) [32]: 'environmental quality standards' means the set of requirements which must be fulfilled at a given time by a given environment or particular part thereof, as set out in Union law. Their recognition and compliance ensures the proper condition of the natural environment in particular and contributes to the general development of such natural environment where environmental quality indicators are factored in. For instance, regarding water «environmental quality standard» means the concentration of a particular pollutant or group of pollutants in water, sediment or biota which should not be exceeded in order to protect human health and the environment (Clause 35, Part 1, Article 2 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy [33]).

The vocabulary source states that the term air quality standards refer to levels of air pollutants prescribed by regulations that may not be exceeded during a specified time in a defined area [34]. In p. 9 of Preamble to Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe [35] it is noted that air quality status should be maintained where it is already good or improved. Where the objectives for ambient air quality laid down in this Directive are not met, Member States should act in order to comply with the limit values and critical levels, and where possible, to attain the target values and long-term objectives. Moreover, this Directive states that «level» shall mean the concentration of a pollutant in ambient air or the deposition thereof on surfaces in a given time (Clause 3, Part 1, Article 2) and «limit value» shall mean a level fixed on the basis of scientific knowledge, with the aim of avoiding, preventing or reducing harmful effects on human health and/or the environment as a whole, to be attained within a given period and not to be exceeded once attained (Clause 5, Part 1, Article 2).

At the theoretical level it is stated that soil quality "the capacity of a soil to function within ecosystem and land-use boundaries to sustain biological productivity, maintain environmental quality, and promote plant and animal health" [36]. Soil quality is an account of the ability of soil to provide ecosystem and society services through its capacities to perform its functions and respond to external influences [37, p. 12]. Soil parameters indicate the state of soil ecosystem characteristics, which especially reflect production, buffering, filter and other soil functions [38]. "Soil quality standards", i.e. maximum permissible total concentrations of pollutants in soils [39, p. 789]. In other words, compliance with the requirements that are benchmarks in maintaining the proper quality of the soil is important. Thus according to para. 2 paragraph 2.1 of Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions – Thematic Strategy for Soil Protection [40]: soil degradation has a direct impact on water and air quality, biodiversity and climate change. It can also impair the health of European citizens and threaten food and feed safety.

Hence, based on the above, environmental quality indicators, being both certain indicators of quality in general and gauges of natural resources in particular are important in recognition of certain processes, which have different

nature of origin and are influenced by this origin directly or indirectly. They, along with other components, affect environmental health. Analyzing the provisions that describe the second set of indicators, which characterize condition of natural environment, while referencing scientific definitions, environmentally responsible behaviour is related to resource and energy savings, use of renewable energy sources, waste sorting and recycling, wastewater disposal etc. [41]. Ergo, these are indicators that reflect the level of awareness in certain performers about the importance of good overall treatment of the environment, and natural environment in particular. On the other hand, the indicators act as specific benchmarks of action or inactivity that would be most useful in a particular situation. According to para. 26 of the Preamble to Directive (EU) 2019/904 of the European Parliament and of the Council of 5 June 2019 on the reduction of the impact of certain plastic products on the environment [42]: economic and other incentives to support sustainable consumer choices and promote responsible consumer behaviour can be an effective tool for achieving the objectives of this Directive. Therefore, the existence of certain means creates the preconditions for responsible environmental behaviour, which has an absolute impact on environmental health. For instance, p. 1 art. 10 of Directive 2019/904 of the European Parliament and of the Council of 5 June 2019 on the reduction of the impact of certain plastic products on the environment: member States shall take measures to inform consumers and to incentivise responsible consumer behaviour, in order to reduce litter from products covered by this Directive. Whereas consumers play a key role in the management of packaging and packaging waste and thus have to be adequately informed in order to adapt their behaviour and attitudes (the Preamble to European Parliament and Council Directive 94/62/EC of 20 December 1994 on packaging and packaging waste [43]), hence, one of the useful steps in implementation of proper behaviour is informing the public and providing it with the necessary information. In addition, in attempt to form environmentally responsible behaviour with regard to establishing of environmental health different technologies are crucial, in particular, namely the ones mentioned in para. (d) p. 1.3.3 part II «Industrial Leadership» of the Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 – the Framework Programme for Research and Innovation (2014-2020) and repealing Decision No 1982/2006/EC Text with EEA relevance [44] is stated about the developing new products and applications, business models and responsible consumer behaviour that reduce energy demand and facilitate low-carbon production.

Regarding the indicators of environmentally responsible behaviour, we should include those that reflect the awareness of the need for appropriate behaviour within relationships between human and natural environment, and, in particular in the rational use of natural resources, recycling and waste re-using etc.

Consequently, by analysing environmentally responsible behavioural indicators as indicators that reflect the essence of environmental health through awareness and internal treatment of the environment in general and the natural environment in particular, that are formed through different means of influence, it can be noted that they create an idea of the necessary behaviour.

The main indicators for the consumption of environmental services and amenities provided are selected on the basis of data provided by Eurostat. These include an index of the sufficiency of sites designated under the EU Habitats Directive, the proportion of terrestrial area protected, total fresh water abstraction per capita, inland fishery products per capita and area of forests and other wooded land per capita [30]. With reference to the vocabulary source environmental services: qualitative functions of natural non-produced assets of land, water and air (including related ecosystem) and their biota. There are three basic types of environmental services: (a) disposal services which reflect the functions of the natural environment as an absorptive sink for residuals, (b) productive services which reflect the economic functions of providing natural resource inputs and space for production and consumption and (c) consumer or consumption services which provide for physiological as well as recreational and related needs of human beings [45, p. 30].

That is, these indicators are related to the specific conditions, which provide the opportunity for proper everyday human activities in the environment that meets the necessary conditions and with the availability of certain resources.

The Union's economic prosperity and well-being is underpinned by its natural capital, i.e. its biodiversity, including ecosystems that provide essential goods and services, from fertile soil and multi-functional forests to productive land and seas, from good quality fresh water and clean air to pollination and climate regulation and protection against natural disasters (p. 17 Annex The 7th Environment Action Programme to 2020 'Living well, within the limits of our planet' [20]).

Consumption leads to the direct creation of environmental pressures from the use of products and services, for example, through driving a car or heating a house with fossil fuels. Of greater magnitude, however, are indirect pressures that are created along the production chains of the goods and services consumed, including, for example, food, clothing, furniture or electricity. Both direct and indirect pressures result in environmental impacts, in particular, global warming, biodiversity degradation, soil sealing and air and water pollution [46, p. 4].

Hence, consumption and, accordingly, its indicators depend on various factors, that are fixed both at the national level by choosing a particular vector of state's actions concerning the environment in general and natural environment in particular, and also human activity, where the certain ways in consumption are chosen on daily basis.

The promotion of more sustainable consumption patterns in the future may be achieved most effectively through the development of sophisticated tailored policy packages that provide a framework that enables consumers, retailers and producers to act more sustainably. Such packages would include well-chosen mixtures of economic incentives, pro-

vision of information to consumers through awareness-raising, labelling and other means, investments in improved infrastructure, technology support, voluntary agreements and where necessary regulation to achieve objectives as effectively as possible [46, p.8-9]. For example, regarding regulation of proper consumption, in para. 16 of the Preamble to Directive 2009/125/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for the setting of ecodesign requirements for energy-related products [47] it is assumed that as a general principle and where appropriate, the energy consumption of energy-related products in stand-by or off-mode should be reduced to the minimum necessary for their proper functioning.

Therefore, proper consumption is manifested in recognition of rational approaches. Those should be reflected in legislation statutes in place in order to legally support their implementation.

CONCLUSIONS

It is hard to disagree with a point of view that was highlighted by one of the authors that each of these groups of indicators are closely interrelated. In particular, these groups of indicators are tightly interrelated as environmentally responsible behaviour has positive impact on environmental quality, and improved environmental quality provides for higher consumption of services provided by the environment [48, p. 11-12]. Undoubtedly, they intersect and thus impact the quality of life, which obviously reflects in indicators of environmental health. Observing and analysing changes in indicators within the outlined issues will allow for the better understanding of that interconnection between the natural environment quality and human health. The appropriate regulatory framework will allow to maintain and improve the natural environment.

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ORCID and contributionship:

Oleksii S. Soloviov: 0000-0002-6615-4868 [A, B, D, F]
Maryna V. Trotska: 0000-0003-3420-0353 [A, B, D, E, F]
Bogdan V. Derevyanko: 0000-0001-7408-828 [B, D, E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Maryna V. Trotska
Department of Constitutional, Administrative,
Environmental and Labour Law, Poltava Law Institute
Pershotravnevy Avenue, 5, 36011, Poltava, Ukraine
tel: +380954909415
e-mail: marinatrockaa@ukr.net

Received: 01.04.2020
Accepted: 23.07.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

CASE STUDY

TWO CASES OF THE CALCIFIED RENAL ARTERY ANEURYSM. DIFFERENTIAL DIAGNOSIS AND TREATMENT (OWN EXPERIENCE)

DOI: 10.36740/WLek202009236

Volodymyr F. Vitkovskyy
LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Renal artery aneurysm is defined as the dilated segment of renal artery exceeding twice the diameter of the normal renal artery. As more than half of such aneurysms have the annular calcification, they must be differentiated from the stones. Differential diagnosis of the renal artery aneurysm includes the parapelvical cysts, hydronephrosis and kidney tumors. Renal artery aneurysm can be diagnosed by CT, MRI, as well by ultrasonography and color dopplerography. Unfortunately presence of calcification renders the ultrasonographic examination impossible. In this article we share our own experience of two cases of calcified renal aneurysms diagnosed and treated at our hospital.

KEY WORDS: renal artery aneurysm, lithotripsy, urography, ultrasonography, dopplerography, nephectomy

Wiad Lek. 2020;73(9 p. II):2097-2100

CLINICAL CASE

Renal artery aneurysm (RAA) is defined as the dilated segment of renal artery exceeding twice the diameter of the normal renal artery [1] According to the autopsy data, incidence of the true renal artery aneurysm is 1 case per 8 000–10 000 autopsies [2, 3]; however the recent results are higher (9,7%) [4]. According to the results of angiography, the incidence of RAA in the general population is 0.3–0.7% [5, 6, 7]; but higher in the patients with hypertension and fibromuscular dysplasia (2.5% and 9.2% respectively) [8, 9]. The most common cause of true RAA (the wall contains all the three layers) is fibromuscular dysplasia and atherosclerosis, whereas the most common etiology of the false aneurysms (the wall doesn't contain the three layers) is iatrogenic trauma and infection. The true RAA are usually located in the main trunk of the renal artery or at its bifurcation, at the same time the false ones dominate in the intrarenal arteries. Size of the aneurysm ranges from the several mm up to 8 cm, the mean diameter is 2.1 cm [10]. Calcified RAA is visible on the KUB in 27–50% cases and can be misdiagnosed as a kidney stone [3, 11, 12].

Diagnosis of RAA can be confirmed or at least suspected by intravenous urography in 66% cases, by the angiography in 100% cases [13]. On the intravenous urography the most common sign is the filling defect or compression of the collecting system, delayed function and asymmetric nephrograms, but the single sign on the KUB can be the annular calcification.

As more than half of RAA have the annular calcification, they must be differentiated from the stones. It's especially important if a lithotripsy has been planned [14]. Sensitivity and specificity to differentiate the vascular lesion and stone of MRI is 78% and 100% respectively, the MRI allows to diagnose the malformation resembling the aneurysm in 91% cases [15].

RAA can be diagnosed by ultrasonography and color dopplerography as well. Calcified RAA looks like the crescent hyperechogenic lesion with the distal hyperechogenic shadow. On the ultrasonography the RAA looks like the hydrogenic mass lesion, containing the turbulent blood flow according to the color dopplerography. Unfortunately presence of calcification renders the ultrasonographic examination impossible. Differential diagnosis of the RAA includes the parapelvical cysts, hydronephrosis and kidney tumors [13, 16, 14, 17].

The urologist must always keep in mind the differential diagnosis between the stone and quite rare calcified aneurysm in order to avoid the major bleeding during the future operation. In this article we want to share our own experience of calcified renal aneurysms diagnosed and treated at our hospital.

Case Report №1. The patient (age 58) was urgently admitted to our hospital with the right-sided renal colic. According to the USG and KUB the patient had the stone (2 cm) of the renal pelvis with hydronephrosis. According to the results of CT we diagnosed the aneurism of the renal artery near the bifurcation causing the hydronephrosis. After the nephrectomy the patient was discharged home. Fig. 1 - 5.

Case Report №2. The woman (age 62) with concomitant arterial hypertension was complaining about the pain in the right back and was sent to the Urological Department with the diagnosis: stone 2 cm of the right kidney established by USG. Accoring to KUB the shadow of stone was situated in the projection of kidney but outside the collecting system.

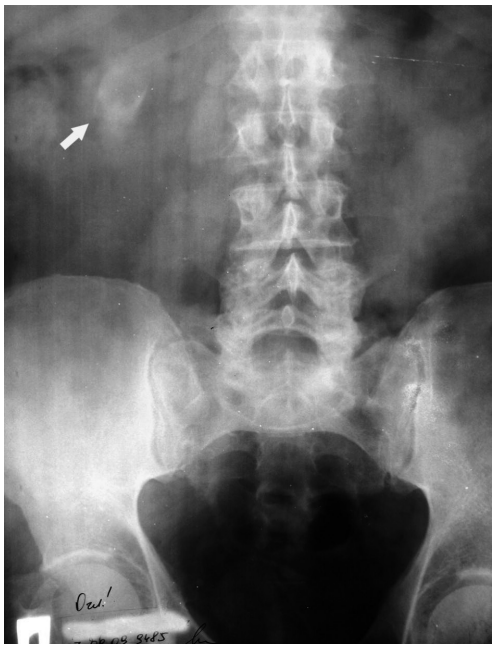

Fig. 1. KUB urography. Radioopaque annular shadow (arrow) in the projection of right kidney.

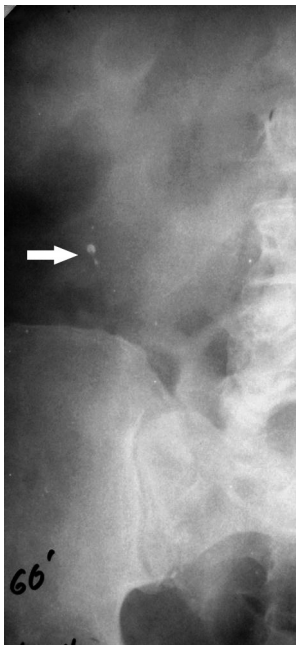

Fig. 2. IVU, 60 min. Contrasted urine is in the bladder. Excretory function of the right kidney is decreased. Radioopaque annular shadow (arrow) is situated in the projection of right kidney.

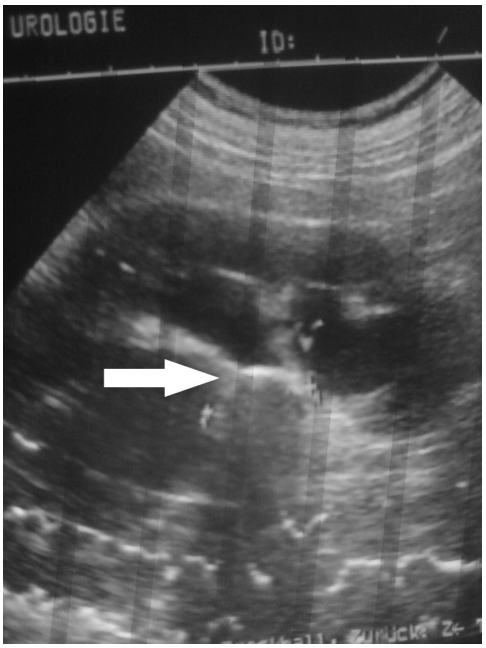

Fig. 3. Ultrasonography: hyperechogec lesion (arrow) with the acoustic shadow resembling the stone in the projection of pelvis of the right kidney, obturating the pelvis and causing the hydronephrosis.

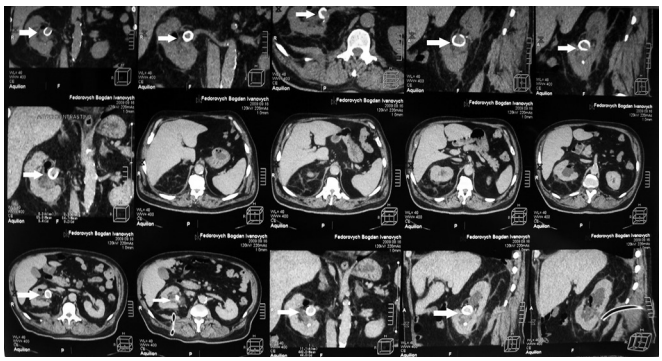

Fig. 4. CT scan: annular calcification (arrow) in the projection of pelvis of the right kidney, at the bifurcation of the right renal artery causing the hydronephrosis. This is the clear criteria for the differentiating the completely calcified aneurysm of the renal artery.

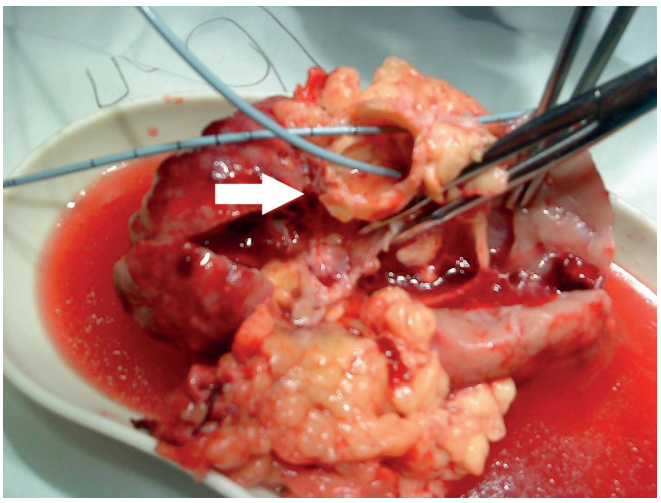

Fig. 5. Removed kidney: the calcified aneurysm (arrow) is widely open with catheters inserted into the proximal and distal part of the right renal artery.

The CT scan reveled the aneurysm at the bifurcation of the renal artery. The patient was transferred to the Department of the Angiosurgery, where the aneurysm was excised and the autotransplantation of the kidney was performed. Fig. 6 – 13.

We analyzed the both cases from the point of view of urologist because the patients were sent to the Urological Department for the operative treatment, in one case urgently with the renal colic.

During the examination by USG and KUB the common finding in the both patients was the symptom of radio-opaque shadow with noncomplete circle, radiolucent in the center. But during the USG these structures were hyperechogenic with acoustic shadow resembling the stone, during the color dopplerography the echosygnal could not penetrate into the aneurysm because of the total calcinosis of the wall.

The USG with dopplerography cannot be the method of first choice of differentiation between the calcified aneurysm and renal stone. Presence the radio-opaque shadow with interrupted circle on KUB is the indication for the CT with contract enhancement, because only this method can distinguish between the kidney stone and calcified aneurysm of the kidney.

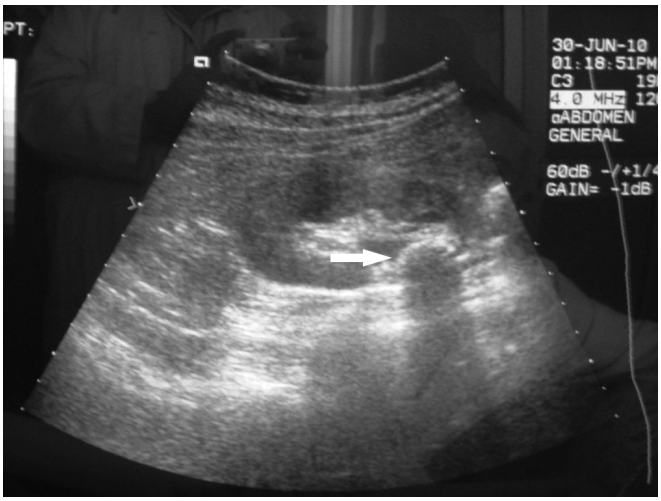

Fig. 6. Ultrasonography: hyperechogenic shadow (arrow) resembles the stone in the projection of pelvis of the right kidney with the acoustic shadow, compresses the pelvis and causes the pyelectasis.

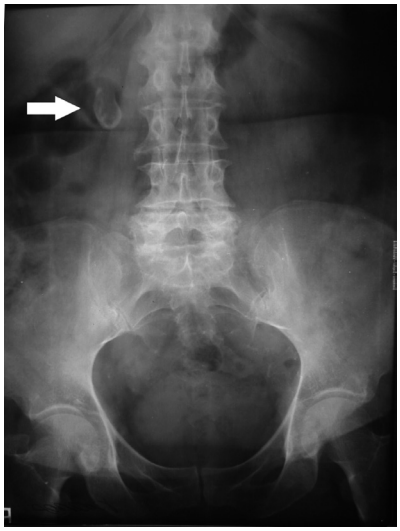

Fig. 7. KUB urography. There is the radioopaque oval shadow (arrow) in the projection of right kidney.

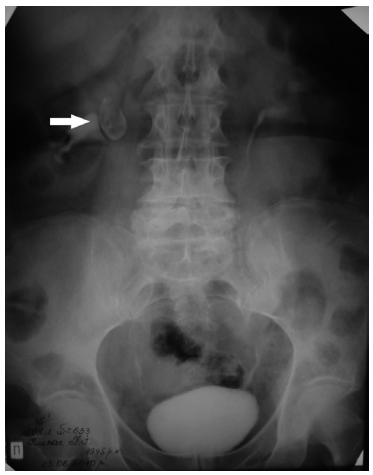

Fig. 8. Intravenous urography, 15 minute: the contrast fills the collecting system of the right kidney, pyelectasis is caused by compression of pelvis and pyeloureteral segment by the radioopaque oval calcified mass lesion (arrow). The excretory function of right kidney is normal

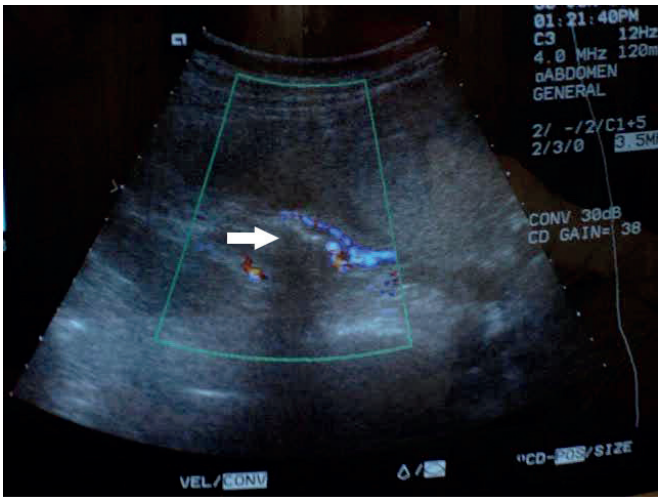

Fig. 9. Ultrasonography with color dopplerography: the hyperechogenic lesion with the acoustic shadow (arrow) resembling the stone is localized in the projection of the right renal pelvis, compressing the pelvis and causing the pyeloectasis. The segmental branch of the right renal artery is situated near the hyperecogenic shadow. Ultrasound cannot penetrate inside the completely calcified aneurysm and confirm the diagnosis; therefore the color dopplerography cannot be used for the differential diagnosis of the calcified aneurysm.

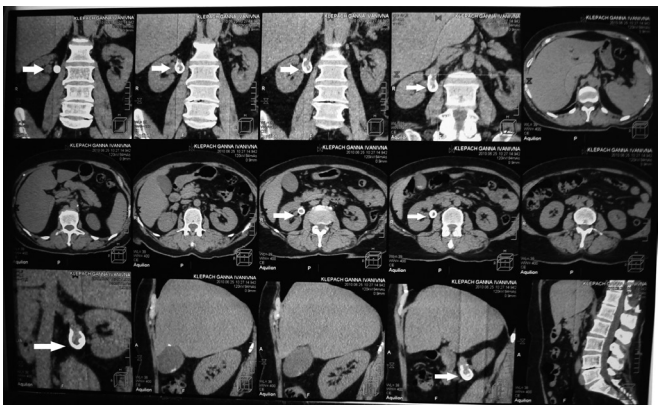

Fig. 10. CT scan: the annular oval-shape calcification is situated near the pelvis of the right kidney at the right renal artery bifurcation, compressing the pelvis and PUJ – this is the differential criterion of the completely calcified aneurysm of the renal artery.

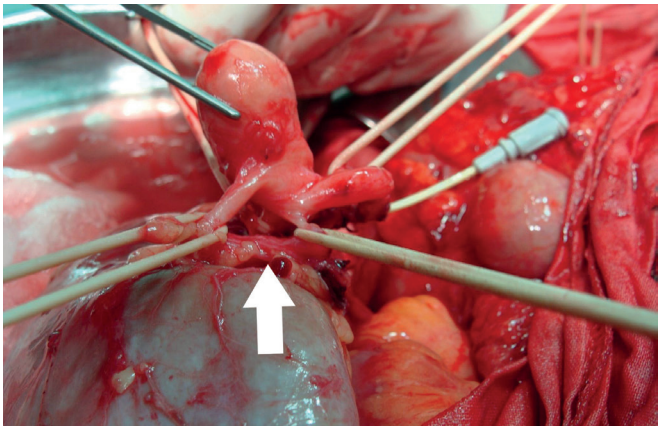

Fig. 11. Operation: autotransplantation of the right kidney with the excision of aneurysm and graphting of the right renal artery. Please note the completely calcified aneurysm (arrow) at the bifurcation. Four segmental branches of the right renal artery are withdrawn by the tourniquets. The central renal artery was excised, through it the catheter was inserted into the kidney in order to wash the blood out. The right kidney was covered by ice.

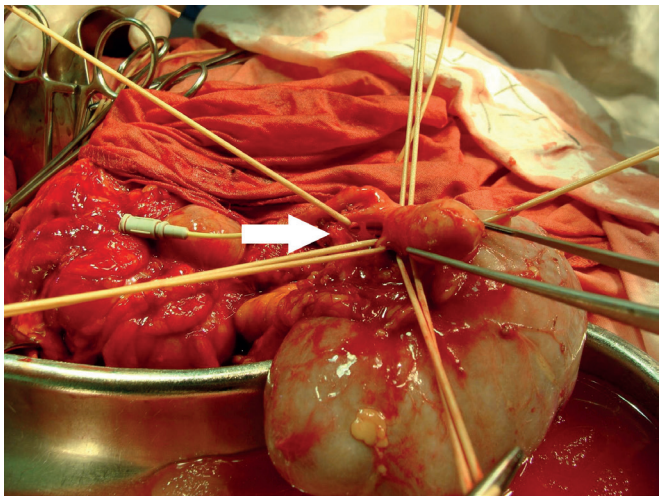

Fig. 12. The picture was taken during the autotransplantation of the right kidney with excision of aneurysm (arrow) and graphting the right renal artery.

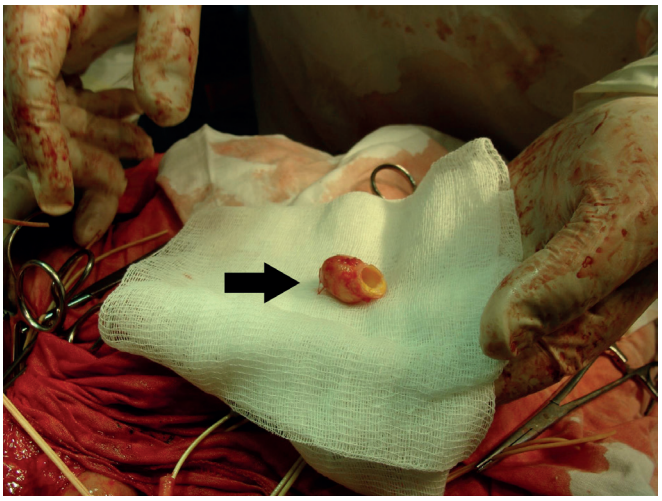

Fig. 13. Picture of the excised calcified aneurysm (arrow) of the right renal artery.

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ORCID and contributionship:
Volodymyr F. Vitkovskyy: 0000-0002-7375-399X [A, B, D, E, F]

Conflict of interest:
The Author declare no conflict of interest.

CORRESPONDING AUTHOR

Volodymyr F. Vitkovskyy
Lviv National Medical University
7 Chernigivska st., 79010 Lviv, Ukraine
tel: +380505880025
e-mail: bohborys@gmail.com

Received: 19.10.2019
Accepted: 30.06.2020

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

CASE STUDY

ARRHYTHMIA IN THE COURSE OF GENERALISED EPILEPSY OF UNKNOWN ETIOLOGY – A CASE STUDY

DOI: 10.36740/WLek202009237

Elżbieta Ewa Szczygieł-Pilut, Anna Zajączkowska-Dutkiewicz
DEPARTMENT OF NEUROLOGY WITH THE SUB-STROKE UNIT AND SUB-DEPARTMENT OF NEUROLOGICAL REHABILITATION, JOHN PAUL II HOSPITAL, CRACOW, POLAND

ABSTRACT

The aim: To draw attention to the need for careful analysis of patients with epilepsy in terms of the possibility of co-occurring arrhythmia.

Material and methods: Analysis of video-EEG registration in the inter-seizure period in a patient with diagnosed epilepsy.

Case study: The authors present a 33-year-old patient with generalised epilepsy of unknown etiology diagnosed in childhood. In this subject, generalised seizure discharges without clinical manifestation of epileptic seizure and with concomitant cardiac arrhythmias in the form of atrial fibrillation were recorded during video-EEG registration. This was carried out during the patient's of hospitalisation at the neurology ward.

Discussion and conclusions: The case study presented is as an example of existing complex and not fully understood interactions between epilepsy and arrhythmia. A mutation within the SCN1B encoding genes, which is responsible for channelopathy within the voltage-dependent Na_v sodium channels, may be considered as a potential cause for this state. However, further analysis and research is needed that would eventually allow to find out the reason for these relationships.

KEY WORDS: epilepsy, arrhythmia, video-EEG registration

Wiad Lek. 2020;73(9 p. II):2103-2119

INTRODUCTION

Arrhythmia is a common and overlooked problem in patients with epilepsy. Often, the diagnosis of epilepsy ends with cardiological diagnostics and vice versa. It is common knowledge that a relationship exists between epileptic seizures and the autonomic function of the heart, however, in clinical practice, it is frequently forgotten that these dysfunctions may coexist [1, 2]. Miakotnykh and Antiuf'ev showed that 64.44% of patients with epileptic seizures have different pathologies in the cardiac stimulus system [3].

Nonetheless, the impact of seizure or status epilepticus on the heart muscle still remains a mystery. These relationships are complex and not fully understood. On the other hand, it is known that epileptic seizures can cause arrhythmias which may be mild, severe or life-threatening. The incidence of sudden death in patients with epilepsy is estimated at 1/1,000. The most frequently reported type of cardiac arrhythmia during an epileptic seizure is sinus tachycardia, which is accompanied by 80% of seizures and is asymptomatic in just over 80% of patients. The analogous parameter in a group of healthy individuals does not exceed 10% [4]. A different but clinically significant arrhythmia found in EEG recordings is asystole. It occurs in 0.318% of people with refractory focal epilepsy [5]. It is often preceded by sinus bradycardia registered in about 6% of cases with focal epilepsy [6, 7, 8]. This problem was noted by Reeves et al. in the journal *Epilepsy.* In 1996, these authors demonstrated that the occurrence of bradycardia should be considered in both the group of patients with syncope as well as epilepsy [9]. Supraventricular tachycardia, atrioventricular block or atrial fibrillation are other potentially dangerous arrhythmias [8, 10, 11].

Arrhythmia often coincides with or may precede epileptic seizures [12]. Inverse situations, i.e. – the occurrence of epileptic seizures preceding the incidence of cardiac arrhythmia such as sinus tachycardia, ventricular fibrillation, bradycardia, asystole, are also frequently reported [13].

To date, the pathophysiology of cardiac arrhythmia in epilepsy has not yet been established. There are a number of hypotheses explaining this dysfunction. Activation or inhibition of cortical autonomic centres, inflammation (IL-6), activation or inhibition of cortical autonomic centres, increase in vagus nerve tension by activation of brainstem reflex centres, respiratory failure, altered ion channel in drug-resistant epilepsy are considered [14]. In the pathogenesis of epilepsy and ventricular arrhythmia, inflammatory processes play a significant role. IL-6 is considered a key mediator of inflammation in the pathogenesis of both disturbances [15]. Increased levels of circulating IL-6 in patients with heart failure as well as in those with epilepsy contributes to the generation of seizures and is positively correlated with the presence of cardiac arrhythmias. Another potentially dangerous cause of death of a patient is the dysfunction of cortical autonomous centres. This is greatly important within the aspect of temporal lobe focal epilepsy most commonly described in adults.

Epilepsy in this area is associated with autonomic instability, which significantly increases the risk of postpartum arrhythmia [16]. Focal stimulation of parts of the limbic system – amygdala, cigulate gyrus may lead to asystole [17-21]. The altered ion channel, especially in the case of drug-resistant epilepsy, may also explain the co-occurrence of cardiac arrhythmias and epilepsy.

Ion channel mutations found in the heart and brain may indicate more susceptibility to both epilepsy and arrhythmia. Some ion channel mutations that have been found in both organs may indicate increased susceptibility to both epilepsy and arrhythmia [22-25].

Therefore, cardiac arrhythmia in epilepsy may result not only from seizure activity, but also from a common genetic susceptibility [4].

The genetic relationship between epilepsy and cardiac arrhythmia has been documented when the cardiac sodium channel gene SCN5A, SCN1B has been found in the brain, and pathogenic variants in the long gene family QT (LQT) (i.e. *KCNQ1, KCNH2* and *SCN5A*) encoding cardiac potassium channels [25-30].

Auerbach DS. et al., in the journal *Neurology* in 2016, analysed mutations in the LQTS 1, LQTS 2, LQTS 3 genes, showing that mutations in the LQTS 2 gene have a predilection both for epileptic seizures and arrhythmia [31].

A mutation within KCNA1, a gene encoding voltage dependent K_v 1.1 potassium channels, resulting in epileptic seizures, can also predispose to bradyarrhythmia, making the KCNA1 gene a potential risk factor for sudden unexpected death among patients with epilepsy [32, 33]. Those especially at risk of SUDEP (Sudden Unexpected Death in Epileptic Patients) are patients with wrongly-controlled or drug-resistant epilepsy.

Of the various phenotypes of voltage-dependent sodium channels responsible for the generation and spreading of action potential in the CNS, especially mutations within encoding genes SCN3A (Na_v 1.3), SCN8A (Na_v 1.6) and SCN1B (Na_v 1.1) are associated with seizure-related disorders, whereby the mutation within SCN1B (Na_v 1.1) may simultaneously imply cardiac channelopathy [26].

Drug therapy among patients with epilepsy is not without influence on heart rhythm. The negative effects on cardiac rhythm in epilepsy have been documented for drugs such as carbamazepine, levetiracetam and lacosamide [34-36].

Adverse reactions to carbamazepine, although rare, may be: conduction disturbances, hypertension or hypotension, as well as bradycardia, arrhythmia or atrioventricular block. In the case of lacosamide, atrial fibrillation and flutter were observed during high dose therapy, around 600 mg/day in patients with epilepsy without significant risk of cardiovascular disease. Phenytoin and phenobarbital are two other drugs, the use of which is associated with a high risk of arrhythmogenic effects in predisposed patients [37]. Phenytoin has a narrow range of therapeutic concentrations (from 10 to 20 μg/mL), and already a slight increase (above 25 μg/mL) may cause signs of toxicity. During therapy with this anti-epileptic drug, it is necessary to monitor ECG recordings, blood pressure, as well as to regularly measure the concentration of the drug in the blood. In the aspect of valproic acid, its potential effect on heart rate cannot be clearly excluded. The drug has a complex mechanism. The most likely action of valproic acid is the selective increase of gamma-aminobutyric acid (GABA) among synapses in the CNS and reduction of GABA consumption by glial cells by activating glutamic acid decarboxylase and inhibition of GABA-transaminase. The drug also affects excitatory neurotransmitters and may affect the sodium and potassium channels in neuronal cell membranes. Similar to valproic acid, there is no clear understanding of lamotrigine's effect on heart rate. Pharmacological results indicate that the drug is a voltage-gated sodium channel blocker. It stabilizes neuronal membranes by inhibiting potential-dependent sodium channels while also blocking the release of excitatory amino acids (glutamic acid).

THE AIM

To draw attention to the need for careful analysis of patients with epilepsy in terms of the possibility of co-occurring arrhythmia.

CASE STUDY

The authors describe the case of a 33-year-old patient diagnosed with generalised epilepsy of unknown etiology in childhood, hospitalised at the Neurology ward to optimize anti-epileptic treatment. Generalised tonic-clonic seizures occurred in the patient at a frequency of 1x/3 months. In the patient's opinion, the number of epileptic seizures had recently increased, they were recorded at a frequency of 1x/month. Before the seizures, the patient felt irritable and experienced weakened concentration preventing from functioning both at work and in everyday activities. The patient complained of impaired concentration and attention accompanied by drowsiness, assuming this was related to the adverse effects of valproic acid. So far, apart from generalised tonic-clonic seizures, no other types were observed in the case of this patient.

The patient took lamotrigine at a dose of 150 mg/day (the level of the drug during hospitalisation was 2.6 L μg/mL) (range of 3-15 μg/mL) and valproic acid at a dose of 2,000 mg/day (the level of valproic acid was 29.3 L μg/mL) (range of 40-100 μg/mL). Pregnancy and perinatal history as well as in the direction of childhood febrile seizures was not burdensome. Family history of sudden cardiac deaths before age 40 was also not applicable. In addition, the patient had not been treated chronically, and had not used any other pharmacotherapy besides anti-epileptic drugs.

In the physical examination, the patient was cardiovascularly and respiratorily stable. No other deviations from the norms were noted. Laboratory diagnostics of thyroid function with assessment of THS concentation, fT_3 and fT_4 were also within the norm. In neurological examination, it was found that: the patient was fully conscious, fully auto- and

allopsychically aware, the pupils were even with a direct and indirect response to light, in the area of other cranial nerves, there were no abnormalities, meningeal and focal symptoms were negative. In MRI of the brain with contrast (with 3 T camera sensitivity in sagittal, frontal, transverse cross-section and thickness layers of 0.9 mm) a single zone of non-specific demyelination in the deep structures of the left island was visualised, and no pathology was shown in the radiological image of the brain.

In the video-EEG, generalised seizure discharges were recorded in the form of spike complexes, slow wave with an amplitude higher than the background of the record compared to normal basal rhythm, without clinical manifestation of epileptic seizure (no occurrence of a seizure), both during and before cardiac arrhythmias were recorded in the ECG record. These disorders persisted throughout the 80-minute video-EEG recording period, independent of the inter-seizure discharges recorded during video-EEG examination. In the video-EEG performed after testing, with a 12-channel ECG, atrial fibrillation and flutter were recorded with a ventricular rate up to 150-160/min, without any other recorded pathologies. No attempts at emergency anti-epileptic or anti-arrhythmic pharmacotherapy were made at the ward.

Both during the current and previous hospitalisations, the patient underwent repeated ECG tests, Holter-ECG monitoring cardiac function – in none of the above were any significant pathologies found.

After cardiological consultation, the patient was directed to a cardiology clinic where detailed diagnostics was performed.

In extensive non-invasive tests: echocardiography, cardiac monitoring by Holter-ECG, stress test, incorrect results were not noted.

The patient, apart from the beta- blocker- bisoprolol at a dose of 1.25 mg/day, did not undergo any special cardiological treatment.

Based on the neuropsychological testing, no impairment of cognitive function was found, the MMPI-2 test was normal.

During hospitalisation, anti-epileptic treatment was modified, and the dose of valproic acid was reduced to a total daily dose of 500 mg. A dose increase of lamotrigine to a total of 200 mg daily was planned. The decision to modify anti-epileptic pharmacotherapy in the manner described above was the result of the patient reporting adverse effects of valproic acid on cognitive functions and pathological drowsiness. The authors of the work also wanted to maintain monotherapy with anti-epileptic drugs acting, among others, via sodium channels. In the 6-month follow-up period after modification of the anti-epileptic treatment, the patient did not experience any epileptic seizures or cardiac events. In the video recording-EEG, paroxysmal changes were not clinically or electroencephalographically observed. Due to the clinical effect of anti-epileptic drugs manifested by the absence of epileptic seizures, blood anti-epileptic drug levels were not measured at that time.

DISCUSSION

The case study described by the authors is another example of existing complex and not fully understood interactions between epilepsy and arrhythmia. Our patient experienced only generalised tonic-clonic seizures, no other types of epileptic seizures were observed. The single zone of non-specific demyelination in the deep insular cortex structure of the left insulae, found in MRI of the head, may have been clinically silent pathological area concerning the aspect of seizure activity, while the arrhythmias resulted from stimulation of the cortex in this location [38]. Nonetheless, the patient remains under clinical observation and in the future, it is possible that we will be able to enrich our knowledge on this subject.

The issue of low blood levels of both AEDs is also under discussion. Based on the medical history (the patient declaring the use of both anti-epileptic drugs as prescribed by the physician), improper intake of medication seems unlikely. Perhaps the low levels of the anti-epileptic drug were due to existing pharmacokinetic variability in particular for valproic acid. The consequence of this in clinical practice should be an increase in the frequency of blood tests for anti-epileptic drugs. However in our patient, during the 6-month follow-up no blood tests for anti-epileptic drugs were made. Therefore, a toxic effect of lamotrigine resulting from the inhibitory metabolism of valproic acid cannot be excluded, neither may it be assumed that increasing the dose of lamotrigine and reducing the dose of valproic acid could have had a neutral effect on the concentration of the first of the listed anti-epileptic drugs.

Our patient, similarly as in the case of the patient described in the work published in the journal Epilepsia in May 2000, Nei M et al. also confirmed ECG abnormalities after and during seizure activity in electroencephalographic recording [6]. In addition, similar as in the work by Herskovitz M et al., published in the journal Arch Neurol. in 2012, our patient arrhythmia in the form of atrial fibrillation appeared as the first symptom of heart disease [39]. Arrhythmias, regardless of seizure activity in electroencephalographic recording, may also have occurred earlier

The fact is that atrial fibrillation is asymptomatic in about 1/3 of cases. It should also be considered whether there is a need for special pharmacotherapy treatment in patients with such a diagnosis.

It seems likely that in the case described by us, we encounter a mutation within the SCN1B encoding genes, which are responsible for channelopathy within the Na_v 1.1 voltage-dependent sodium channels both in the CNS and the heart [26]. Already in 2002, Maier et al. proved that individual sodium channel isoforms physiologically present in the CNS play an important role in both the initiation and conduction of cardiac action potential (Na_v 1.5) as well as in coupling the depolarisation of cardiomyocytes with their contraction (Na_v 1.1, Na_v 1.3 and Na_v 1.6) [40].

Considering the main mechanism of action, in the case of epileptic seizures, the most effective of the sodium channel blockers are phenytoin, carbamazepine and lamotrigine.

Research results prove that lamotrigine is a blocker of voltage-dependent sodium channels, simultaneously

inhibiting discharges and reducing the excitability of the neuronal membrane [41].

Confirmation of our assumption is the 6-month observation period of our patient on modified lamotrigine therapy (as a well-known non-selective Na_v inhibitor), which provided a satisfactory clinical effect, i.e. lack of observed epileptic seizures. This indicates the rightness decision regarding modification of anti-antiepileptic pharmacotherapy.

In the article, there is no unambiguous answer to the question regarding the reason for the documented relationship between arrhythmias and epilepsy. Epilepsy, as a disease entity, should therefore be seen as a complex of symptoms, and all co-morbidities, even the most inconspicuous ones, should be considered as part of stratification and phenotyping in people with such a diagnosis. There is a need for further clinical trials that would allow to ultimately develop optimal strategies. In addition, predictors/markers initiating the onset of epileptic seizures may be established in the future [6]. In this manner, the authors wanted to highlight the problem concerning the co-occurrence of cardiac arrhythmias discussed for many years in patients with epilepsy in the aspect of the growing interest in diagnosing ion channel subunit functions in this group of patients.

CONCLUSION

The diagnosis of epilepsy with concomitant cardiac arrhythmias provides the basis for a more rational diagnosis and therapy of epilepsy taking into account ion channel defects.

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ORCID and cotributionship
Elżbieta Ewa Szczygieł-Pilut – 0000-0002-9290-9312 [A, B, D-F]
Anna Zajączkowska-Dutkiewicz – 0000-0002-1303-2074 [B, D-E]

Conflict of interest
Authors declare no conflict of interest

CORRESPONDING AUTHOR
Elżbieta Ewa Szczygieł-Pilut
Oddział Neurologii z Pododdziałem Udarowym
i Pododdziałem Rehabilitacji Neurologicznej,
Krakowski Szpital Specjalistyczny im. Jana Pawła II,
ul. Prądnicka 80, 31-202, Kraków, Poland;
tel: 00 48 12 614 20 00
e-mail: eszczygiel@vp.pl

Received: 04.06.2020
Accepted: 08.09.2020

VARIA

IS IT WORTH EXAMINING EEG FUNCTION IN PEOPLE UNDERGOING ORTHOPAEDIC SURGERY?

DOI: 10.36740/WLek202009238

Paweł Piotr Dobrakowski[1], Jarosław Szyszka[2]
[1]PSYCHOLOGY INSTITUTE, HUMANITAS UNIVERSITY IN SOSNOWIEC, SOSNOWIEC, POLAND
[2]ORTHOPEDIC SURGERY DEPARTMENT, OPOLE REHABILITATION CENTER, KORFANTÓW, POLAND

ABSTRACT

The vast majority of hip or knee arthroplasty finishes with improved limb functional status. Despite this, some patients do not recover; they "save" the operated limb; they cannot trust it. This also happens in patients whose range of motion and muscle strength are rated as very good. It is possible, therefore, that the causes must be located in the movement initiating centre, in the motor cortex. We can link the activation and changes in the metabolism of the cerebral cortex, e.g. during limb movement, with the changes in bioelectrical activity visible in electroencephalography (EEG).
Conclusions: Our literature analysis shows that so far, no study has been conducted to check whether EEG activity changes over the sensory-motor region after lower limb arthroplasty. We propose the design of such a study with an analysis of potential difficulties that would have to be overcome by the team undertaking the challenge. The obtained data could be the basis for neurorehabilitation using the EEG biofeedback method. Effective interventions would further improve the quality of life.

KEY WORDS: EEG, lower limb, hip joint, knee joint, arthroplasty

Wiad Lek. 2020;73(9 p. II):2108-2122

More and more hip and knee arthroplasty procedures are probably associated with the ageing of the population. In 2005-2017, according to the data of the National Health Fund, 506,911 hip arthroplasty and 173,015 knee arthroplasty were performed. There is a clear tendency to increase the number of performed procedures every year [1].

Osteoarthritis, especially the hip and knee joints, is one of the leading causes of pain and reduced mobility after 45 years of age. It causes disability and reduces the quality of life [2]. There are many discrepancies between objective and subjective assessments of osteoarthritis. Therefore the frequency of occurrence in European countries, varies depending on the methodology used. It ranges from 4 to 27%; the relationship with age is visible [3].

Patients undergo arthroplasty treatment and benefit from rehabilitation. The vast majority of procedures end with the improvement of the functional state of the limb [4]. Despite this, some patients do not recover completely; they "save" the operated limb; they cannot trust it. This also happens in patients whose range of motion and muscle strength are rated as very good. It is possible, that the cause is located in the movement initiating centre, in the brain motor cortex. We can link the activation and changes in the metabolism of the cerebral cortex, e.g. during limb movement, with changes in bioelectrical activity visible in electroencephalography (EEG) [5].

The first results describing the changes in the EEG signal bandwidth (decrease in alpha rhythm power) associated with the stimulus-response were described in Adolf Beck's dissertation entitled "Determination of localization in the brain and spinal cord by electrical phenomena" [6]. Quantitative studies of EEG signal modulation phenomena in response to stimuli were undertaken nearly a hundred years later. Beginning with Pfurtscheller's work, these phenomena began to be called Event-Related Desynchronization (ERD) – i.e. event-related desynchronization [7]. The term ERD refers to a decrease in the power of the bioelectric spectrum in a given EEG band.

The motor cortex of the brain is spatially organized, which means that impulses to move the limb should always come from the same areas. Cortical location of ERD patterns is the result of the somatotopic organization of the sensory and motor cortex. In this arrangement, the representation of the limb is in the primary motor cortex and is generally crystallized.

Over the sensorimotor cortex, we observe the SMR rhythms (Sensorimotor Rhythms) in the EEG recording, for example, oscillations of 8–11 Hz (mu) and 12–30 Hz (beta) [8].

In SMR range it is possible to register ERD or Event-Related Synchronization (ERS), which are directly related to the proportional power loss in motor execution (ME) / motor imagery (MI) of the limb or the increase in signal strength at rest. The ME task is based on the physical movement of the limbs that activate the motor cortex. It includes a change in muscle tone, spasm or flexion [9]. In turn, MI is a cognitive process based on kinesthetic imagination without muscle activity, also called "Kinesthetic Motor Imagery (KMI) [10]. The advantage of MI signals is that they are free of proprioceptive feedback, as opposed to ME tasks.

Assessing bioelectrical activity above the sensory-motor cortex during movement (or its image) of the upper limb has been popular in recent years [11-13]. The literature on similar issues for the lower limb is sparse. This is probably because the representation area of the lower limb is deep in the longitudinal cleft within the sensory-motor cortex (Penfield and Boldrey, 1937). However, research in this direction is ongoing. It has been shown so far that the analysis of beta induction ERS or mu-beta ERD has improved the distinction between left and right foot imaging as accurately as for upper limbs [14]. To our knowledge, no literature is available on the unequivocal application of KMI tasks for the knee or hip joint except [9, 15]. The second reason for the disproportion may be an easier limitation of motor artefacts when examining the upper limb.

Our literature analysis shows that so far, no study has been conducted to check whether EEG activity changes over the sensory-motor region after lower limb arthroplasty. We searched Pubmed, IEEE Explore and Science Direct databases for a combination of passwords: EEG, SMR, ERD, lower limb, knee joint, hip joint, and arthroplasty.

Designing such research meets many potential difficulties that would have to be overcome by the team taking on the challenge.

Interdisciplinary team. Necessarily an orthopaedic specialist who can assess the efficiency of the operated joint before surgery. A specialist in electroencephalography, an expert in quantitative and qualitative EEG analysis. Good statistical background.

Scheduling trials during which the test will be recorded. Effective arthroplasty and proper rehabilitation should result in functional improvement. It would be best to evaluate the EEG changes in dynamic tests, such as walking on the treadmill, climbing stairs, getting up from a chair. Here, however, EEG artefacts from traffic may be in the way. This is one of the most severe restrictions, blocking even EEG registrations in athletes. Numerous attempts are being made to remove motion artefacts from the raw EEG signal. One of them is the method that can be used during rhythmic gait [16]. However, we are afraid that gait in people requiring endoprosthesis surgery will not be synchronous. Maybe cutting out artefacts from gait would be possible thanks to video EEG synchronization.

Another essential choice will be the electrode system for signal registration. There are dry and wet electrodes. Dry electrodes seem very tempting for the above application. They do not require the use of special conductive gels. Thanks to this, preparation for the examination is faster and more comfortable. The gel may also flow out while the object is moving and lose its properties over time [17]. If wet electrodes were chosen, it is worth choosing a thicker gel than the standard one or consider adhesive and conductive paste for fewer artefacts from agitation.

If the above methods would not sufficiently limit EEG artefacts during dynamic tests, the use of imaginary tests could be an interesting solution. Due to the existence of a mirror neuron system, even when thinking about movement, activity within the somatosensory cortex should increase. Asking the patient to imagine, e.g. climbing stairs or balancing on a balance beam may be a good option. The importance of cerebral cortex activation in the image of locomotor tasks has already been described in several papers [18, 19]

Preparing the survey for people with reduced mobility. It will be important to provide adequate space prepared for people with mobility disabilities. Standard sets for EEG recording are quite high. It may be necessary to prepare several stairs with a handrail. Equally important would be handrails in the vicinity of the patient during dynamic tests and patient belaying by the investigators.

The right number of patients. Since in the proposed study, all people would be after endoprosthesis, it is not necessary to calculate the minimum number of people in the sample. However, in order to be able to carry out reliable statistical analyses, at least 30 people after hip surgery and 30 people after knee surgery are needed.

It will also be important to determine if there will be left-footed people among the respondents. In people with right-sided lateralization, the left side of the sensorimotor cortex activates during dominant limb movement. The situation is complicated when a person is moving with the left limbs. In addition to activating the right side cortex, the left side cortex is also activated. This is because it is more fluent in a given traffic pattern and somehow "suggests" how to perform it most economically. Recent studies show that increased activity of the contralateral and ipsilateral cortex can be demonstrated regardless of the limb being moved [20].

In our opinion, it is worth undertaking the proposed analysis, despite many potential difficulties. The obtained data could be the basis for neurorehabilitation using the EEG biofeedback method. Effective interventions would further improve the quality of life.

We wonder if the results for patients after hip and knee surgery would be different. This can be expected even because of the difference in proprioception innervation in these joints [21, 22].

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ORCID and contributionship

Paweł Piotr Dobrakowski – 0000-0002-6436-2487 [A-B,D-F]
Jarosław Szyszka – 0000-0002-5293-8362 [A-B,D-F]

Conflict of interest

Authors declare no conflict of interest.

CORRESPONDING AUTOR

Paweł Piotr Dobrakowski
Psychology Institute, Humanitas University in Sosnowiec
ul. Kilińskiego 43, 41-200, Sosnowiec, Poland;
tel.: +48 506018622
e-mail: paweldobrakowski@interia.pl

Received: 11.07.2020
Accepted: 14.09.2020

LETTER TO EDITOR

DYSAUTONOMIA IN INHERITED PARKINSON DISEASE

Zbigniew K. Wszolek, Łukasz Milanowski
NEUROLOGY, MAYO CLINIC, UNITED STATES

KEY WORDS: dysautonomia, Parkinson disease, genetics

Wiad Lek. 2020;73(8):2111-2113

Dear Editor,

We read with great interest the excellent article by Dutkiewicz and Friedman [1]. The authors critically reviewed the available literature for the diagnosis of autonomic dysfunction, also known as *dysautonomia*, in Parkinson disease (PD). Dysautonomia includes many different medical conditions caused by autonomic nervous system failure, and is among the most important nonmotor symptoms in PD, present in 14% to 80% of PD cases [2-4].

Dysautonomia has also been seen in inherited forms of PD, which occur in approximately 5% to 10% of patients with PD [5,6] Here, we briefly discuss dysautonomia in the most common monogenic forms of PD.

Dysautonomia in PD gene mutations differs among affected patients [6]. Some pathogenic PD mutations have only been reported in a single family, making general assessment difficult. In addition, the description of dysautonomia in these studies is only clinical, without more objective measures such as tilt test, autonomic reflex screening, (123)I-metaiodobenzylguanidine (123MIBG), and others [6].

Dysautonomia is probably best characterized in *SNCA* mutation carriers. Occurrence of orthostatic hypotension and tachycardia were reported in 11 of 21 patients with *SNCA* triplications [7]. *SNCA* duplications are not fully penetrant, but 15 of 44 symptomatic patients with *SNCA* duplication had orthostatic hypotension with cardiac sympathetic denervation and reduced cardiac 123MIBG uptake [7]. Of the 60 individuals known to be affected with Contursi kindred with p.Ala53Thr *SNCA* mutation, dysautonomia was reported in only 1. However, later analyses of 22 additional families (dysautonomia data available for 26 patients) that shared the same p.Ala53Thr *SNCA* mutation revealed that orthostatic hypotension, urinary incontinence, and central hypoventilation were present in 6 of 26 patients [8]. Dysautonomia was reported in most patients with p.Gly51Asp and p.Glu46Lys *SNCA* mutations. However, data were collected only in single families with these mutations (dysautonomia reported in 3/3 and 4/5) [6].

LRRK2 mutations are the most common cause of autosomal dominant PD worldwide. The clinical phenotype seen in carriers with the *LRRK2* mutation is similar to that seen in patients with idiopathic PD. In a Japanese study, only 1 patient out of 5 had reduced 123MIBG cardiac uptake, and a Spanish clinical study comparing 33 *LRRK2* patients with 33 sporadic PD patients found no difference in urinary and gastrointestinal dysfunction [9, 10].

A rare mutation associated with autosomal dominant PD is *VPS35* p.Asp620Asn, with reports of orthostatic hypotension and constipation similar to those observed in patients suffering from idiopathic PD [11]. *CHCHD2* mutations are also a rare cause of autosomal dominant PD. In the first Japanese study, 2 of 12 affected family members had orthostatic hypotension [12], which was also observed in another *CHCHD2* study (7/13 patients) [13].

Autosomal recessive PD is characterized by an early age of onset, usually before age 50. *PRKN* is the most frequently reported autosomal recessive PD gene, and patients usually have a tremor-dominant PD subtype. Dysautonomia is uncommon in *PRKN* homozygotes/compound heterozygotes [14]. *PINK1* is the second most frequently reported mutation in autosomal recessive PD. Both clinical phenotype and occurrence of dysautonomia are similar to those in patients with PRKN. These patients usually exhibit orthostatic hypotension and urinary dysfunction in about 22% and 44% of cases, respectively [14]. In yet another extremely rare form of autosomal recessive PD—in this instance, due to *VPS13C* homozygous/compound heterozygous mutations—affected patients develop urinary dysfunction early in the disease course and usually before 40 years of age [15].

SNCA and *VPS13C* are associated with the most severe dysautonomia compared to other forms of genetically inherited PD. Dysautonomia is not the main nonmotor feature in *PRKN*, *LRRK2*, and *VPS35* mutations (Table 1); rather, its presence and frequency is most likely affected by the different cellular mechanisms leading to compromise in cell function in these genes. Systematic and prospective studies of dysautonomia in other genetic forms of PD are warranted.

Table 1. Autonomic Dysfunction in Different Monogenic Forms of PD

Gene	Mutation	Dysautonomia	Methodology	Reference
SNCA	p.Ala53Thr	Severe (6/26 patients)	Cardiac sympathetic denervation (6-[18F] fluorodopamine-derived radioactivity)	[6]
	p.Gly51Asp	Severe, early-onset orthostatic hypotension (3/3 patients)	Clinical evaluation	[6]
	p.Glu46Lys	Severe (4/5 patients)	Cardiac sympathetic denervation (123MIBG)	[6]
	Duplications	Mild, similar to sporadic PD (15/44 patients, including orthostatic hypotension with fainting, urinary incontinence, constipation, and erectile dysfunction)	Cardiac sympathetic denervation (123MIBG)	[7]
	Triplication	Severe, similar to multiple system atrophy (11/21 patients [6 orthostatic hypotension, 5 urinary incontinence])	Cardiac sympathetic denervation (6-[18F] fluorodopamine-derived radioactivity); heart-to-mediastinum ratio (123MIBG)	[7]
LRRK2	p.Glu2019Ser	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[10]
VPS35	p.Asp620Asn	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[11]
PRKN	Homozygous/ compound heterozygous	Mild, similar age of onset and frequency to sporadic PD	Cardiac sympathetic denervation (123MIBG)	[14]
PINK1	Homozygous/ compound heterozygous	Mild, similar frequency to sporadic PD; urinary dysfunction most frequently observed (44% in all autonomic dysfunctions reported); reduced 123MIBG uptake in left ventricle reported	Cardiac sympathetic denervation (123MIBG)	[16]
VPS13C	Homozygous/ compound heterozygous	Early age of onset, severe orthostatic hypotension, even ≤40 (2/3 patients)	Clinical evaluation	[15]

Abbreviations: 123MIBG, (123)I-metaiodobenzylguanidine scintigraphy; PD, Parkinson disease.

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ORCID
Zbigniew K. Wszolek - 0000-0001-5487-1053
Łukasz Milanowski - 0000-0003-4197-8518

Acknowledgments
L.M. is supported by the Polish National Agency for Academic Exchange Iwanowska's Fellowship PPN/IWA/2018/1/00006/U/00001/01, and by the Haworth Family Professorship in Neurodegenerative Diseases fund. Z.K.W is partially supported by the Mayo Clinic Center for Regenerative Medicine, the gifts from The Sol Goldman Charitable Trust, and the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases fund, and The Albertson Parkinson's Research Foundation. He serves as PI or Co-PI on Biogen, Inc. (228PD201) grant, and Biohaven Pharmaceuticals, Inc. (BHV4157-206 and BHV3241-301). He serves as PI of the Mayo Clinic American Parkinson Disease Association (APDA) Information and Referral Center, and as Co-PI of the Mayo Clinic APDA Center for Advanced Research.

CORRESPONDING AUTHOR
Zbigniew K. Wszolek
Neurology, Mayo Clinic,
4500 San Pablo Rd, 32224, Jacksonville, United States
tel: Phone: 904-953-8173
e-mail: wszolek.zbigniew@mayo.edu

Dear Professor Wszolek, dear Doctor Milanowski,

we are glad that our article "Diagnostics of autonomic disorders in Parkinson's disease" aroused your interest. Your letter added a new aspect of dysautonomia being sometimes related to genetic mutations in PD.

Autonomic dysfunction deserves special attention, as it is a troublesome complaints of many of our patients. Thank you for such an interesting response to our article.

Yours sincerely,
Andrzej Friedman, Justyna Dutkiewicz

Informacja prasowa Warszawa, 12 października 2020 r.

Pulmonolodzy włączają się w akcję zdrowego oddechu dla Polski. Inauguracja akcji „Drzewa od Teva" w Kazimierzu Dolnym.

Zanieczyszczenie powietrza jest przyczyną niemalże co drugiej (43%) choroby płuc i co trzeciego (29%) zgonu z powodu nowotworu płuc[1]. Tymczasem Polska jest jednym z najbardziej zanieczyszczonych krajów w Europie[2]. Inauguracja akcji „Drzewa od Teva" w Kazimierzu Dolnym, podczas znanej naukowej konferencji, rozpoczyna ogólnopolskie działania mające na celu redukcję śladu węglowego powstającego w wyniku produkcji leków.

Polska jest w Europie jednym z krajów o najbardziej zanieczyszczonym powietrzu[2]. 33 z 50 europejskich miast z wysoce przekroczonymi normami znajdują się w naszym kraju[2]. Oprócz redukcji emisji, dobrym sposobem na walkę z zanieczyszczeniami jest zalesianie, ponieważ drzewa działają jak naturalne filtry powietrza – usuwają cząstki stałe i dwutlenek węgla (CO_2) z atmosfery, a wraz z nimi absorbują pyły zawieszone PM10[2]. Dlatego też, w trosce o zdrowy oddech Polaków, firma Teva rozpoczęła szeroką akcję sadzenia drzew w Polsce. Inauguracja programu odbyła się w Kazimierzu Dolnym, który jest tradycyjnie już od 20 lat miejscem jesiennych Konferencji Alergologów, Pulmonologów i Immunologów Klinicznych.

„Zostaliśmy zaproszeni do zainaugurowania ogólnopolskiej akcji „Drzewa od Teva". Z ogromnym przekonaniem włączamy się w tę inicjatywę, która ma na celu poprawę jakości powietrza w naszym kraju" – mówi **prof. dr hab. n. med. Andrzej Emeryk, Przewodniczący Komitetu Naukowego i Organizacyjnego XXI Kazimierskich Spotkań z Alergologią i Pulmonologią** – *„Jako specjaliści chorób płuc i układu oddechowego, jesteśmy szczególnie zainteresowani działaniami proekologicznymii edukacyjnymi w tym zakresie."* – dodaje.

Eksperci z obszaru pulmonologii zasadzili pierwsze w akcji drzewa, które stworzą piękną klonową aleję przy ulicy Senatorskiej w Kazimierzu. W ramach inicjatywy „Drzewa od Teva", do końca 2020 roku Teva planuje zasadzić w sumie 100 000 drzew. W pierwszej kolejności, już w październiku, tam, gdzie są najbardziej potrzebne - na terenie nadleśnictw kaszubskich, które najbardziej ucierpiały po klęsce nawałnicy w 2017 roku. Kolejne tysiące drzew zostaną zasadzone w roku kolejnym, w miejscach uzgodnionych z zarządcami lasów.

„Celem akcji „Drzewa od Teva" jest poprawa jakości powietrza w naszym kraju przez sadzenie drzew na terenie całej Polski. Obok produkcji wysokiej jakości leków, naszą misją są działania poprawiające zdrowie i samopoczucie ludzi. Realizujemy ją na wiele sposobów, w tym także promując odpowiedzialne zachowania i realizując programy pozytywnie wpływające na środowisko. Jedną z naszych ambicji jest redukcja tzw. śladu węglowego, związanego z produkcją leków w naszej fabryce. Poza stale udoskonalanymi metodami produkcji, realizujemy ten cel sadząc drzewa." – **wyjaśnia Michał Nitka, Dyrektor Generalny Teva Pharmaceuticals na region Europy Centralnej i Wschodniej.**

Kontakt dla mediów:
Anna Załuska
kom: +48-601145935
Anna.Zaluska@teva.pl

Przypisy końcowe

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