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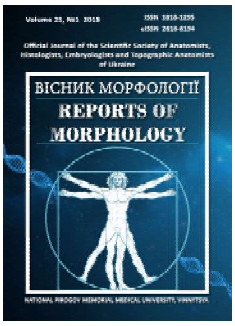

Morphological features of radioiodine-resistance metastases of thyroid papillary carcinoma

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An important problem in the diagnosis, treatment and prediction of papillary thyroid cancer is radioiodine-resistant metastases, early prediction of which is possible on the condition of determining their cytological and histological characteristics. The purpose of this work was to identify the histological and cytological characteristics of metastases of papillary thyroid carcinomas correlated with their iodine-accumulative capacity, on the basis of which it will be possible to predict the radio-resistance of papillary thyroid carcinomas. A cytological examination of punctates of 30 papillary carcinomas and 45 of their metastases identified in the postoperative period and analysis of the histological characteristics of 100 papillary carcinomas of the general population, 47 primary papillary carcinomas and their radio-resistant metastasis and 17 primary papillary carcinomas of patients with radioiodine-uptake metastases were conducted. Statistical analysis was performed via the non-parametric criterion χ^2 in the package Statistica 11.0. It has been shown a statistically significant difference between presence of sign of follicular structures in the histological material of primary papillary cancer of patients with radioiodine-resistance metastases and between of primary papillary cancer of patients with radioiodine-uptake metastases and common population of papillary thyroid cancer. It has been shown a statistically significant difference between punctuates of radioiodine-resistance and radioiodine-uptake metastases in presence of such cytological characteristics as different subpopulations of thyrocytes. It has been shown that the cytological characteristics of radioiodine-resistant metastases differ from radioiodine-uptake metastases and primary papillary carcinomas by the presence of different subpopulations of thyrocytes, particular structures and oxyphilic changes. It is shown that such histological characteristics as lack of follicular structures in the material of primary papillary carcinomas correlate with radio-resistance and can be prognostic factors of its appearance.

Key words: *thyroid papillary carcinoma, fine-needle aspiration puncture biopsy, radioiodine-resistant metastasis, cytological characteristics, histological signs.*

Introduction

As a result of the accident at the Chernobyl Nuclear Power Plant, there was a sharp increase in the incidence of thyroid gland (TG) cancer. The highest increase in the level of thyroid cancer was observed among subjects whose age at the time of the accident was 18 years and younger. So, four years after the Chernobyl disaster, the incidence of thyroid cancer in children increased by 4.8 times, and in subsequent years exceeded the accident rate by 10 times [3, 9, 23]. However, in contrast to carcinoma of other localizations, differentiated thyroid cancer in most cases has a favorable prognosis: the survival 5-year rate of patients with thyroid cancer is about 98%, and 20-30 years of survival exceeds 90% [10, 14, 15]. The key to successful treatment of differentiated thyroid cancer and its metastases is the use of radioiodine therapy, a specific highly effective, targeted method of treating this disease. Radioiodine therapy is based on the unique features of the physiology of thyroid cells that are able to accumulate radioiodine and use it in the synthesis of thyroid hormones. But, unfortunately, in some cases (4-20%), in patients with differentiated thyroid carcinoma, on the background of thyroidectomy and radioiodine therapy, metastases whose cells lose the ability to accumulate radioiodine develop appear: this tumor is called metastatic radioiodine-

refractory disease [11, 12, 13]. It is these metastases that cannot be treated with radioiodine therapy and can be uncontrolled to spread in the patient's body and even be the cause of his death [5, 6, 7]. Therefore, it is important to study the immunocytochemical, genetic and morphological features of such metastases. There are some ideas about the histological manifestations of radioiodine resistance [8, 21, 25]. The most aggressive types of thyroid papillary carcinoma (PC) researchers consider high-cellular, columnar-cellular, diffuse-sclerosing, solid and widely invasive follicular variants [19]. According to the literature, some pathomorphological features of primary TG carcinoma correlate with the effectiveness of radioiodine therapy. The loss of sensitivity of the tumor to the radioiodine is thought to result in a reduction in the differentiation of its cells. The manifestation of this phenomenon is the appearance of elements of low degree of differentiation in metastatic tumors of such patients. Such attributes include such pathomorphological characteristics as solid tumor structure, cell oxyphilia, necrotic changes, high numbers of mitoses [20]. Despite the existing literature data on the histological characteristics of thyroid carcinoma with aggressive behavior, there was no clear correlation between histologic peculiarities and thyroid radioiodine resistance.

The earliest possible prediction of radioiodine resistance of papillary thyroid carcinoma is possible on the basis of the determination of the cytological characteristics of the cells of the radioiodine resistant metastases (RIRM). However, no literature data on similar cytological studies have not been found. Therefore, the *purpose* of this work was to study the histological and cytological characteristics of metastases of papillary carcinoma of the thyroid gland (PC TG), correlated with their iodine-accumulation ability, on the basis of which it will be possible to predict the radioiodine resistance of PC TG.

Materials and methods

In this work, the material obtained as a result of performing fine-needle aspiration puncture biopsy in male and female patients from the age of 17 to 40 years old who were examined surgical treatment and radioiodine therapy in the clinic of our institute were used. The specified protocol used to treat patients with thyroid cancer consists of radical thyroidectomy and lymphadenectomy, postoperative radioiodine therapy in 4-6 weeks and the appointment of suppressive hormone therapy with L-thyroxine (2.5 μg/kg). Conducting of scintigraphic and sonographic research allowed to detect in the postoperative period radioiodine-resistant metastases of PC TG and metastases capable of accumulation of radioiodine. In all cases, the diagnosis was confirmed cytologically and histologically (except for radioiodine-sensitive metastases, which were successfully treated with radioiodine and in most cases, they were not surgically removed).

According to the decision of the Bioethics Commission, SI "V.P. Komisarenko Institute of Endocrinology and Metabolism of NAMS of Ukraine" (No. 28/1-KE of April 12, 2019) found that the study followed ethical and moral requirements, was safe for the patient's health and did not deny the basic bioethical norms of the Helsinki Declaration, the Council of the Convention Europe on human rights and biomedicine, as well as relevant provisions of the WHO and the laws of Ukraine.

Cytological studies were performed on punctures of 30 PC TG detected prior to thyroidectomy and at punctures 45 metastases of PC TG, which arose in the postoperative period following total thyroidectomy and radioiodine therapy. The punctures were fixed with methanol for 5 minutes and stained using the Romanowsky method for 30 minutes. A solution for staining was prepared from a Romanowsky concentrate produced by the Shostka Chemical Reagent Plant consisting of: 20 ml phosphate buffer 0.07 M (pH = 6.4), 1,5 ml of Romanowsky stain.

The analysis of pathological findings of 47 primary PC of patients with RIRM, their RIRM, 17 patients with radioiodine susceptible metastases (RISM) and 100 PC of the general population were carried out. In the group of patients with RIRM, three of them had a diagnosis of "diffuse sclerosing variant of PC TG", 31 with primary thyroid PC (PPC) (66%) had invasive growth in the capsule and beyond, metastases to regional lymph nodes. The histological study was carried out in the laboratory of pathomorphology of the SI "Department of Endocrinology and Metabolism" (head of the department - MD, Prof. Bogdanova T.I.).

The statistical processing of the data was done according to a non-parametric criterion χ^2, which allows comparing the frequency of occurrence of the qualitative characteristics studied in two samples. The calculations are made in the Statistica package 11. If the sign occurs in any of the comparison groups in less than 10 cases, the Yates correction for continuity was used.

Results

A comparative study was performed on the presence of certain histological characteristics in the pathomorphological findings of the following tumor groups - PPC of patients who developed with time RIRM, the PPC of patients with RISM, the general population of thyroid PC and the RIRM group. The presence of such histological signs, which according to the literature was related to the aggressive behavior of PC-follicular structures (FS), necrotic changes (NC) and oxyphilic-cellular changes (OC), was analyzed.

The presence of FS was noted in the histological conclusions of the PPC TG in 20% of patients, in which developed RIRM. At the same time, RIRM of these patients had a papillary or papillary-solid structure, and FS were found in only 1 case (2%). In this case, in the general population of PC TG, FS were found in 60% of cases (30 times more often than in the group RIRM and 3 times more often than in PPC patients with such metastases). In this case, in the PPC group with RISM, FS were found in 70% of cases. According to the non-parametric criterion χ^2, a statistically significant

difference at the significance level p<0.05 was confirmed by the presence of a morphological sign - FS between the PPC group of patients with RIRM and PPC in the group of patients with RISM (p = 0.002), between the PPC group of patients with RIRM and the general population PC TG (p = 0.000), and between the PPC of patients with RIRM and the RIRM group (p = 0.010, with the Yates correction for continuity). Thus, the statistically significant difference between the PPC with RIRM and the PPC with RISM and the general group of PC demonstrates that the absence of FS is associated with the development of RIRM and may be a worrying prognostic factor in the development of radioiodine resistance of PC TG.

In the analysis of the presence of the following histological sign, the OC in the pathologist's conclusions, it was found that the frequency of its intolerance in the PPC patients with RIRM (30%) was slightly higher than in the overall population of PC TG (16%), slightly higher such as in the PPC TG of patients with RISM (23%) and RIRM group (21%). There was no statistically significant difference in the incidence of OC between the PPC patients with RIRM and PPC in patients with RISM (p = 0.859 with Yeats correction), and in the PPC patients with RIRM and the general population of PC (p = 0.053). That is, there was no correlation between the presence of this histological sign and the radioiodine resistance of the tumors under investigation.

Although the presence of histological signs of necrotic changes (NC) of the tumor is associated with the "adverse behavior" of thyroid tumors, the literature does not give a clear idea of its correlation with the ability of thyroid carcinoma precisely to accumulate radioiodine. Therefore, we conducted a comparative analysis of the incidence of NC in all of the above groups of tumors.

As a result of the performed research, it was found that the incidence of NC in the control group of patients with RIRM was higher (2%) than in the general population of PC (1%). In this case, NC did not register in the PPC patients with RISM, and in the group RIRM NC were also noted in 2 cases. The statistical analysis carried out did not reveal a significant difference in the frequency of NC exposure between the PPC patients with RIRM and the PPC with RISM (p = 0.593 with Yeats correction), and between the PPC with RIRM and the general population of PC (p = 0.831). The results of the research are shown in the table (Table 1).

Table 1. Frequency of occurrence of the following histological signs - FS, NC and OC in primary thyroid PC of patients with RIRM and RISM, the general population of the PC and RIRM.

Sign	PPC patients with RIRM	RIRM	Total population PC	PPC patients with RISM
FS	20% *	2%	60%	70%
NC	2%	2%	1%	0%
OC	30%	21%	16%	23%

Notes: * p<0.05 in comparison with the general population of the PC, the PPC patients with RISM by the criterion χ^2.

Thus, the statistical analysis of the research has shown that the factor of absence of FS in the primary PC can be an alarming histological prognostic factor for the appearance of RIRM PC TG. At the same time, the presence of NC and OC in the primary tumor is not associated with the growth of radioiodine resistance.

Since there was no literature data on cytological research of RIRM PC TG, we have conducted comparative studies of cytological characteristics of the thyroid cells population in punctates of RIRM, RISM and the corresponding PPC TG. The performed studies showed that in the punctures of RIRM in 2 times more frequent than in their PPC there are different subpopulations of thyroid cells (which are cytologically different from the general population of thyroid cells), OC are more common, and in 10% - there are specific cellular structures that consist of a psammoma bodies surrounded by a layer of macrophages and vacuolated epithelial cells (Fig. 1).

At the same time, in all cases, the cytological characteristics of RISM are not different from their PPC, their cytograms are represented by regular epithelial layers, which

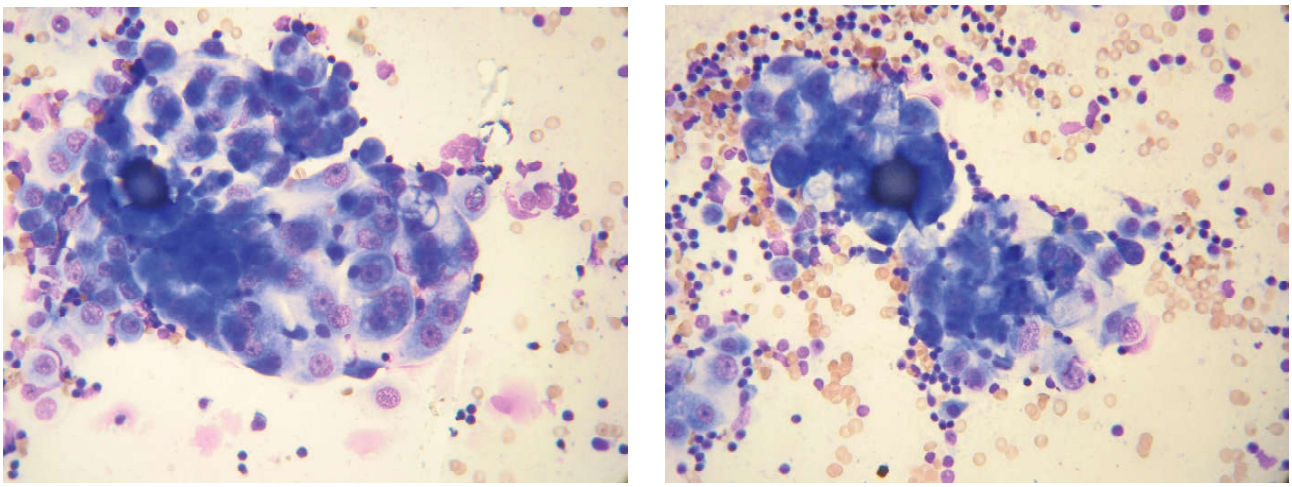

Fig. 1. Special complexes of psammoma bodies and surrounding thyroid cells with signs of expressive vacuolation in RIRM PC TG punctate. Romanowsky staining. Objective x40, eyepiece x3.3.

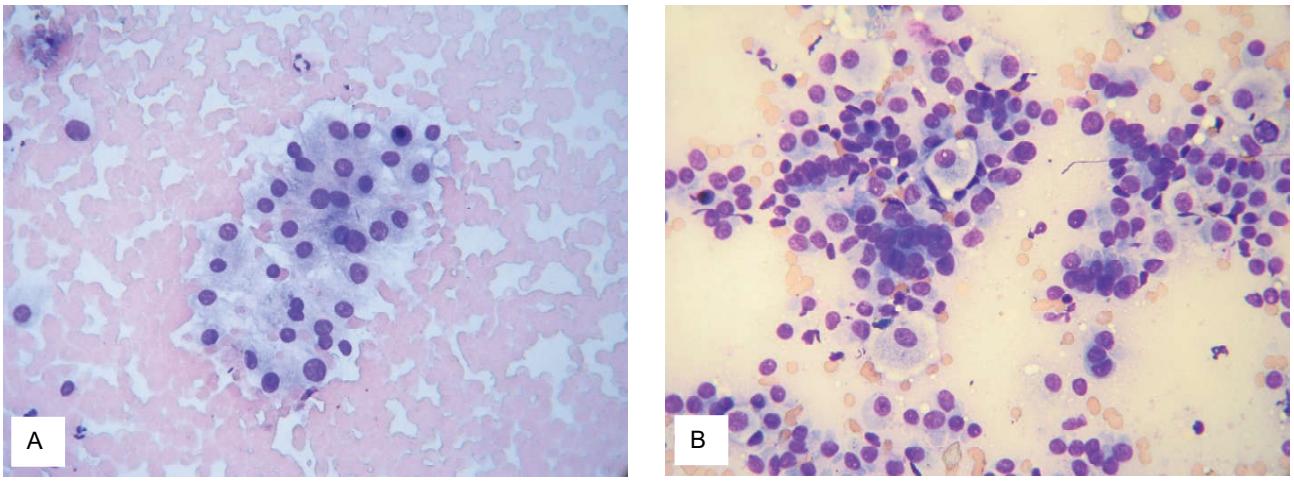

Fig. 2. A - homogeneous population of thyroid cells without expressive signs of atypia in the RISM PC TG punctate. B - different subpopulations of thyroid cells (large rounded cells with clear contour on the background of moderately enlarged thyroid cells) in the RIRM PC TG puncture. Romanowsky staining. Objective x40, eyepiece x3.3.

Table 2. The frequency of various cytological signs in the RIRM and RISM PC TG punctates and the punctates of the corresponding PPC.

Types of thyroid cells	Patients with RIRM (n=30)		Patients with RISM (n=15)	
	PPC	RIRM	PPC	RISM
Different subpopulations	36,6% *	79,9% *#	0%	0%
Special complexes	0%	10%	0%	0%
OC	16,6%	26,6% *	0%	0%

Notes: * - $p<0.05$ in comparison with RISM by criterion χ^2; # - $p<0.05$ in comparison with the PPC by criterion χ^2.

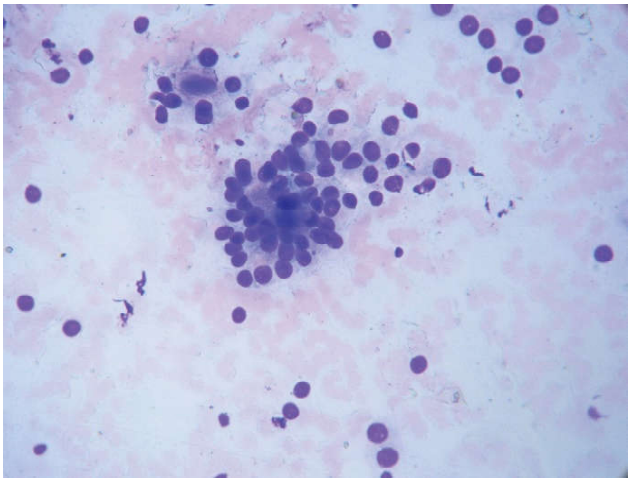

Fig. 3. Follicular structures in the RIRM PC TG punctate. Romanowsky staining. Objective x40, eyepiece x3.3.

consist of homogeneous thyroid cells, in which there are no different subpopulations of cells, OC and special structures. The punctate cells of the PPC and RISM had no signs of a marked atypia, only showing signs of proliferation of the follicular epithelium (Fig. 2, Table 2).

Another interesting observation concerns the follicular structures (FS), the presence of which is considered a prerequisite for the accumulation of radioiodine. In spite of the fact that in the histological material of RIRM FS were noted only in the first case, we observed FS with colloid within 14% of RIRM punctures, which gives grounds to consider the absence of follicles as a pathomorphological, rather than cytological, manifestation of radioiodine resistance of PC TG (Fig. 3).

Discussion

Radioiodine resistance of PC TG is the biggest problem in the diagnosis and treatment of differentiated thyroid cancer. Since RIRM cannot be detected with a conventional scintigraphic study, it is important to be warned about the possible development of radioiodine resistance of papillary thyroid cancer, which gives the chance to timely use of additional research methods and treatments like carcinoma. Early prediction of the radioiodine resistance of PC TG is possible in the presence of histological and cytological features of such metastases. There are literary data [24] regarding some histological manifestations of aggressive behavior and radioiodine resistance of TG carcinoma, but there are no data on cytological studies of RIRM PC TG.

Complex researches and analysis of cytological and histological characteristics of PPC and their metastases, depending on their iodine accumulation ability, have allowed to reveal morphological peculiarities of metastases associated with radioiodine resistance of PC TG. It is shown that among the studied histological characteristics of tumors, only the absence of FS in the histological material of the PPC is associated with the development of their radioiodine resistance. The fact of loss of FS in the development of RIRM PC TG can be regarded as a manifestation of a reduction in the degree of differentiation resulting in the progression of the tumor. Such data are confirmed in the literature and indicate that TG carcinomas that lose FS, lose the ability to effectively concentrate and store iodine for a long time (for example, solid state metastases) [2]. The absence of FS in

the histological material of the PPC can be considered as an alarming factor in predicting their radioiodine resistance. An interesting phenomenon of the absence of FS in the histological material of RIRM (except for 1 case), when they are registered in 14% of punctures of RIRM can be explained by the fact that when conducting a FNAPB RIRM, even single follicles, which do not mark histologists, can enter into the punctate.

According to literature, tumor necrosis factor is one of the most important histologic markers of poorly differentiated PC and an independent predictor of survival of the patient, even when the histologic tumor architecture corresponds to a well-differentiated PC [14]. At the same time, we did not find a statistically significant difference in the frequency of occurrence in the histological material of such signs as NC and OC between the study groups of tumors. Accordingly, these factors cannot be considered as associated with the development of radioiodine resistance PC TG.

Since the cytological characteristics of the RIRM PC TG were not yet found, we conducted a comparative cytological study of RIRM, RISM and related PPC. It is shown that the RISM cytograms and their control groups have no distinct differences and are represented by homogeneous populations of thyroid cells without expressive signs of polymorphism and atypia. At the same time, RIRM differ in a heterogeneous population of thyroid cells, among which there are different types of cells, including enlarged thyroid cells with a clear cell surface. Different subpopulations of cells are found in punctates of RIRM 2 times more often, and OC is 1.6 times more frequent than in the PPC. The difference in the frequency of the occurrence of different subpopulations of thyroid cells in the punctates between the RIRM and their PPC and RISM is statistically proved. Attention is drawn to the special complexes of psammoma bodies and vacuolated cells that occur in 10% of RIRM and are not found in PPC and RISM. Similar to these complex structures in large numbers are presented in the histological material of the diffuse-sclerosing variant of PC, which, according to literature and our observations, is one of the most aggressive variants of PC TG. It is possible that such special structures may be candidates for the title of cytological prognostic factors of radioiodine resistance PC TG.

The presence in PC TG punctates of the RIRM of a greater diversity of cellular subpopulations and thyroid cells structures compared with the RISM group may be a manifestation of their greater genetic heterogeneity, which may be a "polygon" for the formation of new thyroid cells subclones, aggressive, may eventually lose its accumulation ability for radioiodine and cause the development of radioiodine resistance. These considerations do not contradict contemporary ideas about clonal cellular evolution and the existence of the phenomenon of intracellular cell heterogeneity, which can be the basis for the development of the resistance of various tumors to therapy [1, 4, 16, 18].

To date, we have not found in available literature data on similar studies of the material of FNAPB of TG in this aspect. In only a few studies in the histological material of the nodal goat, heterogeneity of the thyroid epithelium population was assessed on the basis of cell proliferative activity [22]. In addition, in studies conducted on the cultivation of some lines of anaplastic thyroid carcinoma, researchers have shown that there is a small cellular subpopulation that has some properties of stem cells [17].

As a result of our research, we have received new representations about the cytological and histological characteristics of PC TG associated with their radioiodine resistance, which may be the basis for developing methods for monitoring the radioiodine resistance and developing personalized approaches to each thyroid cancer patient.

The obtained data on the cytological characteristics of RIRM (the presence of various subpopulations of thyrocytes, special cellular structures in comparison with RISM) may become the basis for the development of new methods for preoperative prediction of radioiodine resistance of PC TG. The obtained data on the histological characteristics of the PC, which correlate with their radioiodine resistance, will allow in the future to predict the behavior of the PC in advance.

Conclusions

1. The statistically probable difference in the presence of a histological sign - follicular structures between primary papillary carcinomas of patients with the development of radioiodine-resistant and radioiodine-sensitive metastases and the general population of papillary carcinomas has been proven, which allows us to consider the absence of follicular structures in the histological material of primary papillary carcinoma as an alarming prognostic factor for the appearance of radioiodine-resistant papillary metastases cancers of the thyroid gland. The lack of follicles is a pathomorphological, rather than cytological manifestation of radioiodine resistance.

2. The presence of necrotic and oxyphilic changes in the histological material of the primary thyroid papillary carcinoma cannot be considered as prognostic factors of radioiodine-resistant.

3. Cytological studies of postoperative metastases were performed for the first time in comparison with primary papillary carcinomas of the thyroid gland, which demonstrated the presence of various subpopulations and structures of thyroid cells in radioiodine-resistant metastases, which were absent in radioiodine-sensitive metastases and primary papillary carcinomas.

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МОРФОЛОГІЧНІ ОСОБЛИВОСТІ РАДІОЙОДРЕЗИСТЕНТНИХ МЕТАСТАЗІВ ПАПІЛЯРНОГО РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Зелінська Г.В.

Важливою проблемою діагностики, лікування та прогнозування папілярного раку щитоподібної залози є радіойодрезистентні метастази, раннє прогнозування появи котрих можливо за умовою визначення їх цитологічних та гістологічних особливостей. Метою роботи було дослідження гістологічних та цитологічних характеристик метастазів папілярних тиреоїдних карцином, корелюючих з їх йод-накопичувальною здатністю, на основі котрих стане можливим прогнозування радіойодрезистентності тиреоїдних папілярних карцином. Було проведено цитологічне дослідження пунктатів 30 папілярних

карцином та 45 метастазів, виявлених у післяопераційному періоді, проаналізовані гістологічні ознаки 100 папілярних карцином загальної популяції, 47 первинних папілярних карцином та їх радіойодрезистентних метастазів, а також 17 первинних папілярних карцином у пацієнтів з радіойодчутливими метастазами. Статистичну обробку отриманих даних проводили в пакеті Statistica 11.0 за непараметричним критерієм χ^2. Вперше були проведені цитологічні дослідження післяопераційних метастазів у порівнянні з первинними папілярними карциномами щитоподібної залози, котрі виявили наявність різних субпопуляцій та структур тиреоцитів у пунктатах радіойодрезистентних метастазів, котрі були відсутніми в радіойодчутливих метастазах та первинних папілярних карциномах. Показана статистично імовірна відмінність в наявності фолікулярних структур в гістологічному матеріалі між первинними папілярними карциномами пацієнтів з радіойодрезистентними метастазами, первинними папілярними карциномами пацієнтів з радіойодчутливими метастазами та загальною популяцією папілярних карцином. Не виявлено статистично імовірної відмінності у наявності некротичних та оксифільних змін в гістологічному матеріалі між всіма досліджуваними групами пухлин. Таким чином, цитологічні характеристики радіойодрезистентних метастазів відрізняються від радіойодчутливих метастазів та первинних папілярних карцином наявністю різних субпопуляцій тиреоцитів, особливих клітинних структур та оксифільно-клітинних змін. Доведено, що відсутність фолікулярних структур в гістологічному матеріалі первинних папілярних карцином може застосовуватися в якості прогностичного фактору появи радіойодрезистентних метастазів.

Ключові слова: *папілярна карцинома щитоподібної залози, тонкоігольчаста аспіраційна пункційна біопсія, радіойодрезистентні метастази, цитологічні ознаки, гістологічні ознаки.*

МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ РАДИОЙОДРЕЗИСТЕНТНЫХ МЕТАСТАЗОВ ПАПИЛЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ

Зелинская А.В.

Важной проблемой диагностики, лечения и прогнозирования папиллярного рака щитовидной железы являются радиойодрезистентные метастазы, раннее прогнозирование появления которых возможно при условии выявления их цитологических и гистологических особенностей. Целью данной работы было выявление гистологических и цитологических характеристик метастазов папиллярных тиреоидных карцином, коррелирующих с их йод-накопительной способностью, на основе которых станет возможным прогнозирование радиойодрезистентности тиреоидных папиллярных карцином. Было проведено цитологическое исследование пунктатов 30 папиллярных карцином и 45 метастазов, выявленных в послеоперационном периоде, проанализированы гистологические характеристики 100 папиллярных карцином общей популяции, 47 первичных папиллярных карцином и их радиойодрезистентных метастазов, а также 17 первичных папиллярных карцином у пациентов с радиойодчувствительными метастазами. Статистическую обработку данных проводили по непараметрическому критерию χ^2 в пакете Statistica 11.0. Впервые были проведены цитологические исследования послеоперационных метастазов в сравнении с первичными папиллярными тиреоидными карциномами, которые выявили наличие разных субпопуляций и структур тиреоцитов в пунктатах радиойодрезистентных метастазов, отсутствующие в радиойодчувствительных метастазах и первичных папиллярных карциномах. Показано статистически достоверное различие в наличии фолликулярных структур в гистологическом материале между первичными папиллярными карциномами пациентов с радиойодрезистентными метастазами, первичными папиллярными карциномами пациентов с радиойодчувствительными метастазами и общей популяцией папиллярных карцином. Не виявлено статистически достоверной разницы в наличии некротических и оксифильных изменений в гистологическом материале между всеми исследуемыми группами опухолей. Таким образом, цитологические характеристики радиойодрезистентных метастазов отличаются от радиойодчувствительных метастазов и первичных папиллярных карцином наличием разных субпопуляций тиреоцитов, особых клеточных структур и оксифильно-клеточных изменений. Доказано, что отсутствие фолликулярных структур в гистологическом материале первичных папиллярных карцином можно применять в качестве прогностического фактора появления радиойодрезистентностных метастазов.

Ключевые слова: *папиллярная карцинома щитовидной железы, тонкоигольчастая аспирационная пункционная биопсия, радиойодрезистентные метастазы, цитологические признаки, гистологические признаки.*

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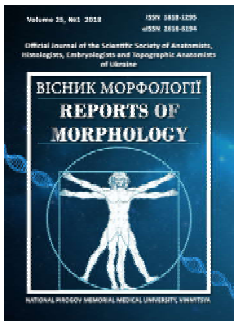

Predictive assessment of the association of dermatoglyphic indicators with indicators of personality traits, established by factor analysis

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According to modern scientific literature, specific dermatoglyphic signs can be diagnostic markers of a person's mental state. The purpose of the work is to identify the association of dermatoglyphic indicators with personality characteristics of practically healthy men of Ukraine. From the data bank of the materials of the research center of National Pirogov Memorial Medical University, Vinnytsya were taken the primary dematoglyphic and questionnaires indicators of personality characteristics of 92 practically healthy men in the third generation residents of Vinnitsya, Khmelnytsky, part of Ternopil and Zhytomyr regions. Processing of dermatoglyphs was performed according to the method of Cummins H. and Midlo Ch. (1961) in the statement by Gladkova T.D. (1966). For objective evaluation of personality traits of practically healthy men, a number of leading indicators were determined, which included a number of properties of temperament (according to Eysenck), anxiety (according to Spielberger), accentuated personality traits (according to Shmishek), motivational orientation of personality (by Rotter), as well as the peculiarities of psycho-emotional organization of personality, aggressiveness, the level of distribution of asthenic and depressive personality manifestations (by the color test of Luscher), which were determined on the basis of personal use personality questionnaires and test methods. Factor analysis was performed in the "Statistica 6.1" license package. The main factors that indicate the association of personality traits of practically healthy men with some dermatoglyphic indicators are identified: "ridge count of fingers" (dispersion ratio - 13.22%) and "atd angle" (dispersion ratio - 10.66%). Analysis of the obtained relationships of the interdependence of indicators of personality characteristics with dermatoglyphic indicators showed that with increasing indicators of ridge counts of the fingers and the delta index the degree of probability of growth of indicators of neuroticism according to Eysenck, situational and personal anxiety according to Spielberger, the accentuation of the character of the emotional and arousing types by Shmishek, subjective control in the field of health and illness according to Rotter, black and gray color by Luscher decreases, and the indicators of the accentuation of the character of the anxious and demonstrative types by Shmishek, the overall internality of the level of subjective control in the field of educational (professional) relations according to Rotter, blue and blue-green color by Luscher - is increasing. As the magnitude of the angle atd increases on both hands, the degree of likelihood of growth of neuroticism according to Eysenck, situational and personal anxiety according to Spielberger, accentuation of the character of the emotional, anxious and arousing types by Shmishek, blue color by Luscher increase, and indicators of accentuation of the character of the demonstrative type according to Shmishek, the general internality of the level of subjective control, in the field of educational (professional) relations and in the field of health and illness according to Rotter, blue-green, black and gray color according to Luscher - decrease. The use of factor analysis has allowed to determine the most significant correlation of indicators of personality characteristics with dermatoglyphic indicators.

Keywords: *dermatoglyphic indices, indices of personality traits, practically healthy men, factor analysis.*

Introduction

Separation of a particular branch of dermatoglyphics - psychodermatoglyphics was the result of numerous works devoted to finding a connection between the peculiarities of the skin pattern and the mental sphere of human life. This branch finds its application for professional profile selection of employees, students, pupils, revealing a tendency to mental illness, creating a psychological portrait for the needs of police, etc. [6, 15, 16].

In 2016, T. Ye. Afonichev, Yu. O. Tyshkovets, and M. V. Filippova [2] conducted an experiment aimed at determining the relationship between the features of skin patterns of finger and the level of student success. 60 students were selected for the study, which were divided into 4 groups according to mental development after passing the Eysenck test. Whorls (32.8 %) were found to be more prevalent in high-intelligence individuals, especially on the left hand. Students with low mental development tend to have loop patterns (65.0 %), and most of them were found on the third and fifth fingers of left and right hands.

210 people enrolled in Lagos (Nigeria) schools were screened to identify specific dermatoglyphic markers of giftedness to one or another type of learning [1]. The respondents belonged to the Yoruba, Igbo and Hausa ethnic groups. The most common among gifted schoolchildren were such elements of patterns as whorls and ulnar loops. Thus, 65 % of schoolchildren who have a gift for music education have a pattern type - whorl. At the same time, ulnar loops on the second finger of the left and right hands were the most characteristic among schoolchildren with a genius for the logical and mathematical sciences.

A similar study that had the same purpose was conducted in 2014 by Kumari K.L., Babu P.V. and Kumar S.V. [18]. This study found only an increase in the number of ulnar loops and a significant prevalence of whorls when examining students studying medical specialties.

The features of skin pattern in depressed individuals have been identified by a group of Chinese scientists [19]. V.O. Tikholaz and Yu.J. Guminsky established the features of dermatoglyphics in patients with paranoid form of schizophrenia depending on the duration of inpatient treatment. When comparing dermatoglyphics data between healthy and diseased individuals, significant differences in both quantitative indexes of palmar and finger dermatoglyphics were revealed [25]. A team of scientists analyzed 22 studies in the period 1968-2012, on the topic of the relationship between indicators of skin pattern and schizophrenia. It has been found that the most frequently mentioned in articles statistically significant indicators were total finger ridge score and the palmar ridge score on the line connecting the tri-radii a-b [12]. A similar study was conducted by a group of Bulgarian researchers, who also point to the priority importance of the index of the palmar ridge score on the line connecting the tri-radii a-b in this disease [3].

The *purpose* of the work is to identify the association of dermatoglyphic indicators with personality characteristics of practically healthy men of Ukraine.

Materials and methods

From the data bank of the materials of the research center of National Pirogov Memorial Medical University, Vinnytsya were taken primary dermatoglyphic indices and personality indicators of 92 practically healthy men (selected after psychophysiological and psycho-hygienic questionnaire and detailed clinical examination) of the first mature age in the third generation residents of Vinnytsiya, Khmelnytsky region, parts of Ternopil and Zhytomyr regions (Podillia region).

Processing of dermatoglyphs was performed according to the method of Cummins H. and Midlo Ch. [8] in the statement by Gladkova T.D. [11].

For objective evaluation of personality traits of practically healthy men, a number of leading indicators were determined, which included a number of properties of temperament (according to Eysenck), anxiety (according to Spielberger), accentuated personality traits (according to Shmishek), motivational orientation of personality (by Rotter), as well as the peculiarities of psycho-emotional organization of personality, aggression, the level of distribution of asthenic and depressive personality manifestations (by the Luscher color test), which were determined on the basis of the use of personality's questionnaires and test methods [9, 10, 13, 17, 20, 22-24].

For the purpose of prognostic assessment of the influence of dermatoglyphic indices on the indices of personality traits of practically healthy men of Ukraine used factor analysis, which was carried out in the licensing package "Statistica 6.1" [5].

Results

For factor analysis, we included all indices of personality traits, indexes of finger and palmar dermatoglyphics, and asymmetry indices of dermatoglyphic indices that have no negative values.

Using the "scree plot", 3 separate factors were identified (Fig. 1).

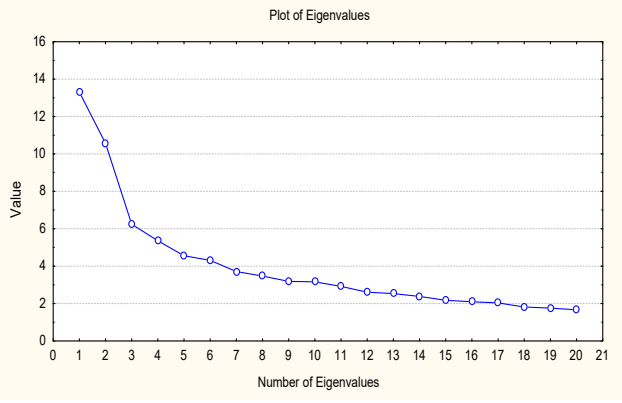

Fig. 1. Select the number of factors with the help of "scree plot".

Table 1. The results of primary data processing using factor analysis.

	Eigenval	% total Variance	Cumul. Eigenval	Cumul. %
1	13.31	11.78	13.31	11.78
2	10.57	9.35	23.88	21.13
3	6.24	5.53	30.12	26.66

Notes: Eigenval - eigenvalues; % total Variance - % of total variance; Cumul. Eigenval - sum of eigenvalues; Cumul. % - accumulated percentage of variance.

As a result of the use of factor analysis for 3 factors, we have established the following main characteristics (Table 1).

Since the eigenvalues of all factors are greater than 1, they have the right to exist by the first criterion for the selection of factors. The total amount of variance is 30.1 %, but the third "part" of the variance is different from the previous one, so it can be abandoned (see Table 1).

Then we calculated the load (correlation coefficients between the original variables and the values of the factors), which allowed us to allocate the most significant load for each factor (Table 2).

Table 2 shows that the first factor includes the quantitative indexes of finger dermatoglyphics, and the second - the magnitude of the angles on the palms.

To maximize the scatter of load squares, we used the Varimax method for each factor (Table 3). When comparing the results with the data in Table 2, we can see that the magnitude of the loadings in the first factor remained practically unchanged. In the second factor, only the magnitude of the atd angle on the right and left palms remained among the most significant loads (see Tables 2, 3).

Taking into account the results obtained, the first factor can be defined as the "ridge count of the fingers" and the second factor - the "angle atd".

The obtained results allow in practically healthy men of Ukraine to define and formalize the interdependence of indicators of personality characteristics with dermatoglyphic indicators in the form of the following relationships: $y_{(AZ\_E)}$ = 0.361f1 + 0.011f2; $y_{(AZ\_N)}$ = -0.084f1 + 0.454f2; $y_{(AZ\_L)}$ = -0.092f1 + -0.185f2; $y_{(SP\_ST)}$ = -0.116f1 + 0.016f2; $y_{(SP\_LT)}$ = -0.057f1 + 0.353f2; $y_{(SH\_G)}$ = 0.089f1 + -0.090f2; $y_{(SH\_Z)}$ = -0.101f1 + 0.408f2; $y_{(SH\_EM)}$ = -0.002f1 + 0.091f2; $y_{(SH\_P)}$ = -0.103f1 + 0.094f2; $y_{(SH\_T)}$ = 0.063f1 + 0.115f2; y(SH_C) = -0.103f1 + 0.386f2; $y_{(SH\_DM)}$ = 0.044f1 + -0.025f2; $y_{(SH\_V)}$ = -0.128f1 + 0.289f2; $y_{(SH\_DC)}$ = -0.055f1 + 0.143f2; $y_{(SH\_EK)}$ = 0.055f1 + 0.370f2; $y_{(USK\_1)}$ = 0.045f1 + -0.364f2; $y_{(USK\_2)}$ = 0.057f1 + -0.311f2; $y_{(USK\_3)}$ = 0.137f1 + -0.303f2; $y_{(USK\_4)}$ = 0.042f1 + -0.291f2; $y_{(USK\_5)}$ = 0.099f1 + -0.120f2; $y_{(USK\_6)}$ = 0.085f1 + -0.272f2; $y_{(USK\_7)}$ = -0.066f1 + -0.122f2; $y_{(LUS\_1)}$ = 0.104f1 + 0.076f2; $y_{(LUS\_2)}$ = 0.133f1 + -0.007f2; $y_{(LUS\_3)}$ = 0.036f1 + 0.057f2; $y_{(LUS\_4)}$ = -0.059f1 + -0.058f2; $y_{(LUS\_5)}$ = -0.060f1 + -0.038f2; $y_{(LUS\_6)}$ = 0.133f1 + 0.017f2; $y_{(LUS\_7)}$ = -0.043f1 + -0.012f2; $y_{(LUS\_8)}$ = -0.287f1 + -0.049f2; where, factor f1 - should be defined as "ridge count of fingers" (proportion of variance - 13.22 %) and is associated with virtually all indexes of the

Table 2. The value of factor loadings indicators of personality characteristics and dermatoglyphics.

Indicators	Factor Loadings (Varimax raw) Extraction: Principal components (Marked loadings are > .700)		Indicators	Factor Loadings (Varimax raw) Extraction: Principal components (Marked loadings are > .700)	
	Factor 1	Factor 2		Factor 1	Factor 2
1	2	3	4	5	6
AZ_E	0.035	0.012	ATD_R	0.010	0.851
AZ_N	-0.103	0.451	AD_R	0.244	0.496
AZ_L	-0.084	-0.189	CT_R	0.226	-0.617
SP_ST	-0.116	0.011	AB_R	0.050	0.482
SP_LT	-0.071	0.350	BC_R	0.095	0.334
SH_G	0.092	-0.086	CTD_R	0.032	0.568
SH_Z	-0.117	0.403	ATB_R	-0.025	0.687
SH_EM	-0.006	0.091	BTC_R	-0.007	0.482
SH_P	-0.107	0.090	CD_R	0.195	0.229
SH_T	0.058	0.118	DAT_R	-0.018	-0.607
SH_C	-0.119	0.381	ATD_L	0.160	0.834
SH_DM	0.045	-0.023	AD_L	0.209	0.515
SH_V	-0.139	0.284	CT_L	-0.008	-0.678
SH_DC	-0.061	0.141	AB_L	0.074	0.461
SH_EK	0.040	0.372	BC_L	-0.030	0.460
USK_1	0.060	-0.362	CTD_L	0.177	0.507
USK_2	0.070	-0.308	ATB_L	0.171	0.703
USK_3	0.149	-0.297	BTC_L	-0.122	0.523
USK_4	0.054	-0.289	CD_L	0.195	0.236
USK_5	0.104	-0.116	DAT_L	-0.169	-0.613
USK_6	0.096	-0.268	IK_R	0.214	-0.156
USK_7	-0.061	-0.125	IK_L	0.101	-0.170
LUS_1	0.101	0.080	HIP_R	-0.153	0.079
LUS_2	0.133	-0.002	TEN_R	0.015	-0.291
LUS_3	0.034	0.059	I_R	-0.057	-0.182
LUS_4	-0.056	-0.060	II_R	-0.072	0.192
LUS_5	-0.058	-0.040	III_R	-0.216	0.186
LUS_6	0.133	0.022	IV_R	0.196	-0.061
LUS_7	-0.042	-0.014	T1_R	0.030	0.684
LUS_8	-0.284	-0.061	T2_R	0.020	-0.635
TF_R1	0.199	0.079	T3_R	0.023	-0.128
FRC_R1	0.697	-0.001	TT_R	-0.076	0.290
TF_R2	0.100	-0.136	HIP_L	0.003	0.173
FRC_R2	0.815	-0.077	TEN_L	-0.012	-0.199
TF_R3	-0.024	0.009	I_L	-0.126	-0.083
FRC_R3	0.828	-0.073	II_L	-0.121	0.289
TF_R4	0.004	-0.388	III_L	-0.091	0.118
FRC_R4	0.774	0.061	IV_L	-0.009	-0.173
TF_R5	0.230	-0.018	T1_L	0.094	0.643
FRC_R5	0.800	0.041	T2_L	-0.043	-0.621

Continuation table 2.

1	2	3	4	5	6
DTR_R	0.840	-0.040	T3_L	0.070	-0.138
SRC_R	0.955	-0.018	TT_L	-0.052	0.327
TF_L1	0.492	-0.062	RL_TF1	0.270	-0.146
FRC_L1	0.712	-0.040	RL_TF2	0.082	-0.106
TF_L2	0.022	0.029	RL_TF3	0.170	-0.021
FRC_L2	0.846	0.094	RL_TF4	0.275	0.119
TF_L3	0.051	0.214	RL_TF5	0.120	0.035
FRC_L3	0.852	0.032	RL_HIP	0.055	0.043
TF_L4	0.388	0.059	RL_TEN	0.035	0.077
FRC_L4	0.813	0.113	RL_I	0.071	0.010
TF_L5	0.283	0.052	RL_II	0.161	-0.047
FRC_L5	0.739	0.154	RL_III	0.267	0.192
DTR_L	0.828	0.029	RL_IV	0.199	0.064
DTR_10	0.879	0.001	RL_T1	-0.172	0.185
SRC_L	0.954	0.079	RL_T2	-0.259	0.077
TRC_10	0.981	0.031	RL_T3	-0.208	-0.042
			RL_TT	0.057	-0.019
			Expl.Var	13.17	10.71
			Prp.Totl	0.117	0.095

Notes: here and in the future, Factor Loadings - factor loadings; Extraction: Principal components - extraction: principal components; Marked loadings are > .700 - marked loadings are >0.700; Factor 1 - factor 1; Factor 2 - factor 2; Expl.Var - the total variance of the factor; Prp.Totl - share of total variance; the most significant loads are highlighted in red; AZ_ - indicators by Eysenck scale (E - extraversion-introversion, N - neuroticism, L - insincerity); SP_ - Spielberger anxiety indicators (ST - situational (reactive) anxiety, LT - personal anxiety); SH_G - indicators of accentuation character by Shmishek (G - hyperthymic type; Z - jamming type; EM - emotional type; P - pedantic type; T - alarming type; C - cyclothymic type; DM - demonstrative type; V - excitable type; DC - dysthymic type; EK - excitable type); USK_ - indicators of the scale of subjective control by Rotter (1 - general internality, 2 - in the field of achievement, 3 - in the field of failure, 4 - in the field of family relations, 5 - in the field of educational (professional) relations, 6 - in the field of interpersonal relations, 7 - in the field of health and illness); LUS_ - indicators of colors by Luscher (1 - blue, 2 - blue-green, 3 - orange-red, 4 - light yellow, 5 - purple, 6 - brown, 7 - black, 8 - gray); _R1 - _R5 - corresponding fingers of the right hand; _L1 - _L5 - corresponding fingers of the left hand; TF_ - the pattern type of the corresponding finger; FRC_ - a local ridge count on each finger; DTR_ - delta index; SRC_ - summary five-finger ridge count; TRC_10 - total finger ridge score; AD_ - the distance between the tri-radii a-d; CT_ - the distance between the tri-radii c-t; AB_ - palm ridge count on line connecting tri-radii a-b; BC_ - palm ridge count on line connecting tri-radii b-c; CTD_ - the size of the angle ctd; ATB_ - the size of the angle atb; BTC_ - the size of the angle btc; CD_ - palm ridge count on line connecting tri-radii c-d; DAT_ - the size of the angle dat; IK_ - index value of major palm lines (Cummins index); HIP_ - the presence of a pattern on the hypotenar; TEN_ - the presence of a pattern on the tenor; I_ - IV_ - the presence of a pattern on the corresponding inter-finger pads; T1_ - the presence of a carpal palm tri-radii; T2_ - the presence of an intermediate palm tri-radii; T3_ - the presence of a central palm tri-radii; TT_ - the presence of several palm tri-radii; RL_ - asymmetry of relevant indicators.

Table 3. The value of factor loadings of indicators of personality characteristics and dermatoglyphics after factor rotation by the Varimax method.

Indicators	Factor Loadings (Varimax normalized) Extraction: Principal components (Marked loadings are > .700)		Indicators	Factor Loadings (Varimax normalized) Extraction: Principal components (Marked loadings are > .700)	
	Factor 1	Factor 2		Factor 1	Factor 2
1	2	3	4	5	6
AZ_E	0.036	0.011	ATD_R	0.045	0.850
AZ_N	-0.084	0.454	AD_R	0.264	0.485
AZ_L	-0.092	-0.185	CT_R	0.201	-0.626
SP_ST	-0.116	0.016	AB_R	0.070	0.480
SP_LT	-0.057	0.353	BC_R	0.109	0.330
SH_G	0.089	-0.090	CTD_R	0.055	0.566
SH_Z	-0.101	0.408	ATB_R	0.003	0.687
SH_EM	-0.002	0.091	BTC_R	0.012	0.481
SH_P	-0.103	0.094	CD_R	0.204	0.220
SH_T	0.063	0.115	DAT_R	-0.043	-0.606
SH_C	-0.103	0.386	ATD_L	0.194	0.827
SH_DM	0.044	-0.025	AD_L	0.230	0.506
SH_V	-0.128	0.289	CT_L	-0.036	-0.677
SH_DC	-0.055	0.143	AB_L	0.093	0.458
SH_EK	0.055	0.370	BC_L	-0.011	0.461
USK_1	0.045	-0.364	CTD_L	0.197	0.500
USK_2	0.057	-0.311	ATB_L	0.200	0.696
USK_3	0.137	-0.303	BTC_L	-0.101	0.527
USK_4	0.042	-0.291	CD_L	0.204	0.228
USK_5	0.099	-0.120	DAT_L	-0.194	-0.606
USK_6	0.085	-0.272	IK_R	0.207	-0.165
USK_7	-0.066	-0.122	IK_L	0.094	-0.174
LUS_1	0.104	0.076	HIP_R	-0.150	0.085
LUS_2	0.133	-0.007	TEN_R	0.003	-0.292
LUS_3	0.036	0.057	I_R	-0.064	-0.179
LUS_4	-0.059	-0.058	II_R	-0.064	0.195
LUS_5	-0.060	-0.038	III_R	-0.208	0.195
LUS_6	0.133	0.017	IV_R	0.193	-0.069
LUS_7	-0.043	-0.012	T1_R	0.058	0.682
LUS_8	-0.287	-0.049	T2_R	-0.006	-0.635
TF_R1	0.202	0.071	T3_R	0.018	-0.129
FRC_R1	0.697	-0.030	TT_R	-0.064	0.293
TF_R2	0.094	-0.140	HIP_L	0.010	0.173
FRC_R2	0.811	-0.110	TEN_L	-0.020	-0.198
TF_R3	-0.024	0.010	I_L	-0.129	-0.077
FRC_R3	0.824	-0.107	II_L	-0.109	0.293
TF_R4	-0.012	-0.388	III_L	-0.087	0.121
FRC_R4	0.775	0.029	IV_L	-0.016	-0.173
TF_R5	0.229	-0.028	T1_L	0.120	0.639
FRC_R5	0.801	0.008	T2_L	-0.069	-0.618
DTR_R	0.838	-0.074	T3_L	0.064	-0.141

Continuation table 3.

1	2	3	4	5	6
SRC_R	0.954	-0.058	TT_L	-0.039	0.329
TF_L1	0.489	-0.083	RL_TF1	0.264	-0.157
FRC_L1	0.710	-0.069	RL_TF2	0.077	-0.109
TF_L2	0.023	0.028	RL_TF3	0.169	-0.028
FRC_L2	0.849	0.059	RL_TF4	0.280	0.107
TF_L3	0.060	0.212	RL_TF5	0.121	0.030
FRC_L3	0.853	-0.003	RL_HIP	0.056	0.040
TF_L4	0.390	0.043	RL_TEN	0.038	0.075
FRC_L4	0.817	0.079	RL_I	0.071	0.007
TF_L5	0.285	0.040	RL_II	0.159	-0.054
FRC_L5	0.744	0.124	RL_III	0.275	0.181
DTR_L	0.829	-0.005	RL_IV	0.201	0.056
DTR_10	0.878	-0.035	RL_T1	-0.165	0.192
SRC_L	0.957	0.040	RL_T2	-0.255	0.087
TRC_10	0.981	-0.009	RL_T3	-0.210	-0.033
			RL_TT	0.057	-0.021
			Expl.Var	13.22	10.66
			Prp.Totl	0.117	0.094

comb finger count (except for the I right finger) as well as the summary, total ridge count and delta index; factor f2 - should be defined as "the magnitude of the angle atd" (proportion of variance - 10.66 %) and includes in its structure only the magnitude of the angle atd of the right and left palms.

Discussion

Uzbek researchers have identified the relationship between the features of dermatoglyphics and personality traits. The results of the data processing showed a relationship between boys' bravery indices and the end of the main palmar line D on the left arm [4].

P. M. Polushkin et al. [21] created a system that allows an accurate portrait of a person to be portrayed with an accuracy of 85 % based on the fingerprints. In the work, boys and girls were divided into groups by temperament, after which they were conducted a dermatoglyphic study.

In recent years, factor analysis has become very popular in biomedical research, which allows us to quantify, for most of the traits under study, a relatively narrow set of properties that characterize associations between these traits and certain generalized factors [5].

When using factor analysis, it was found that, in practically healthy men of Ukraine, factors such as "ridge finger count" (13.22% dispersion angle) and "atd angle" (10.66% dispersion ratio) are most often associated with personality traits.

Analyzing the relationships obtained by the interdependence of personality traits (which have the highest predictive value in terms of human personality formation - AZ_N, SP_ST, SP_LT, SH_EM, SH_T, SH_DM, SH_V, USK_1, USK_5, USK_7, LUS_1, LUS_2, LUS_7 and LUS_8) with dermatoglyphic indicators by factor analysis, it should be noted:

with *increasing* the indexes of the ridge count of the fingers (except for the I finger of the right hand), as well as the summary, total ridge counts (characterize the capacity of the patterns - normal, the more complex the pattern, the higher the ridge count [14]) and delta index (characterize the intensity of the ridge formation [14]) the degree of probability of growth of indicators Z_N, SP_ST, SP_LT, SH_EM, SH_V, USK_7, LUS_7 and LUS_8 *decreases* and SH_T, SH_DM, USK_1, USK_5, LUS_1, and LUS_2 - *increases*;

with *increasing* the magnitude of the angle atd (depends on the localization of the tri-radii a and d at the base of the fingers II and V and axial tri-radii t; consider that the decrease in the palmar angle reflects a decrease in viability and is associated with a number of diseases that exclude longevity [7]) on both palms the degree of probability of growth of indicators AZ_N, SP_ST, SP_LT, SH_EM, SH_T, SH_V, and LUS_1 *increases*, while SH_DM, USK_1, USK_5, USK_7, LUS_2, LUS_7, and LUS_8 - *decreases*.

Thus, the use of factor analysis made it possible to determine the most significant relationship between personality traits and dermatoglyphic indices.

Conclusions

1. When conducting factor analysis identified the main factors that have a significant impact on the characteristics of personality traits of practically healthy men - "ridge count of fingers" (proportion of variance - 13.22 %) and "the magnitude of the angle atd" (proportion of variance - 10.66 %).

2. Analysis of the obtained relationships of interdependence of indices of personality characteristics that have the most predictive value in terms of personality formation of a person with dermatoglyphic indices showed that with *increasing* indexes of ridge counts of fingers and delta index the degree of probability of *increase* in indices of neuroticism by the Eysenck, situational (reactive) and personal anxiety by Spielberger, accentuation of the character of the emotional and arousing types according to Shmishek, subjective control in the field of health and *diseases* by Rotter's, black and gray color according to Luscher decreases, and indicators of accentuation of the character of alarming and demonstrative types according to Shmishek, general internality of the level of subjective control and in the field of educational (professional) relations according to Rotter, blue and blue-green colors by Luscher - *increases*; as the magnitude of the angle atd increases on both palms, the degree of probability of growth of indicators of neuroticism according to Eysenck, situational (reactive) and personal anxiety according to Spielberger, accentuation of the character of the emotional, anxious and arousing types by Shmishek, blue color by Luscher *increase*, and indicators of accentuation of the

character of the demonstrative type by Shmishek, the general internality of the level of subjective control, in the field of educational (professional) relations and in the field of health and illness according to Rotter, blue-green, black and gray color according to Luscher - *reduced*.

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ПРОГНОСТИЧНА ОЦІНКА АСОЦІЙОВАНОСТІ ДЕРМАТОГЛІФІЧНИХ ПОКАЗНИКІВ З ПОКАЗНИКАМИ ОСОБЛИВОСТЕЙ ОСОБИСТОСТІ, ВСТАНОВЛЕНА ФАКТОРНИМ АНАЛІЗОМ

Серебреннікова О.А., Гунас В.І., Клімас Л.А., Очеретна Н.П., Шаюк А.В.

Резюме. *Згідно з даними сучасної наукової літератури специфічні дерматогліфічні ознаки можуть бути діагностичними маркерами психічного стану людини. Мета роботи - виявити асоційованість дерматогліфічних показників з показниками особливостей особистості практично здорових чоловіків України. Із банку даних матеріалів науково-дослідного центру Вінницького національного медичного університету ім. М.І. Пирогова взяті первинні дематогліфічні показники та анкети показників особливостей особистості 92 практично здорових чоловіків у третьому поколінні мешканців Вінницької, Хмельницької, частини Тернопільської та Житомирської областей. Обробку дерматогліфів проводили за методикою Cummins H. і Midlo Ch. (1961) у викладі Гладкової Т.Д. (1966). Для об'єктивної оцінки особливостей особистості практично здорових чоловіків було визначено ряд провідних показників, до складу яких віднесли цілий ряд властивостей темпераменту (за Айзенком), тривожності (за Спілбергером), акцентуйованих рис особистості (за Шмішеком), мотиваційної спрямованості особистості (за Роттером), а також особливостей психоемоційної організації особистості, агресивності, рівня поширення астенічних і депресивних особистісних проявів (за колірним тестом Люшера), які визначали на підставі використання особистісних опитувальників і тестових методик. Факторний аналіз проведений у ліцензійному пакеті "Statistica 6.1". Визначено головні чинники, які свідчать про асоційованість особливостей особистості практично здорових чоловіків з деякими дерматогліфічними показниками: "гребінцевий рахунок пальців кистей" (частка дисперсії - 13,22%) і "величина кута atd" (частка дисперсії - 10,66%). Аналіз отриманих взаємовідношень взаємозалежності показників особливостей особистості з дерматогліфічними показниками показав, що при збільшенні показників гребінцевих рахунків пальців кистей та дельтового індексу ступінь ймовірності зростання показників нейротизму за Айзенком, ситуативної та особистісної тривожності за Спілбергером, акцентуації*

характеру емотивного й збудливого типів за Шмішеком, суб'єктивного контролю в галузі здоров'я та хвороби за Роттером, чорного і сірого кольору за Люшером зменшується, а показників акцентуації характеру тривожного і демонстративного типів за Шмішеком, загальної інтернальності рівня суб'єктивного контролю і в галузі навчальних (професійних) відносин за Роттером, синього і синьо-зеленого кольору за Люшером - збільшується. При збільшенні величини кута atd на обох долонях ступінь ймовірності зростання показників нейротизму за Айзенком, ситуативної і особистісної тривожності за Спілбергером, акцентуації характеру емотивного, тривожного і збудливого типів за Шмішеком, синього кольору за Люшером збільшується, а показників акцентуації характеру демонстративного типу за Шмішеком, загальної інтернальності рівня суб'єктивного контролю, в галузі навчальних (професійних) відносин і в галузі здоров'я та хвороби за Роттером, синьо-зеленого, чорного і сірого кольору за Люшером - зменшується. Застосування факторного аналізу дало можливість визначити найбільш значущі взаємозв'язки показників особливостей особистості з дерматогліфічними показниками.

Ключові слова: *дерматогліфічні показники, показники особливостей особистості, практично здорові чоловіки, факторний аналіз.*

ПРОГНОСТИЧЕСКАЯ ОЦЕНКА АССОЦИИРОВАННОСТИ ДЕРМАТОГЛИФИЧЕСКИХ ПОКАЗАТЕЛЕЙ С ПОКАЗАТЕЛЯМИ ОСОБЕННОСТЕЙ ЛИЧНОСТИ, УСТАНОВЛЕННАЯ ФАКТОРНЫМ АНАЛИЗОМ

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Резюме. *Согласно данным современной научной литературы специфические дерматоглифические признаки могут быть диагностическими маркерами психического состояния человека. Цель работы - выявить ассоциированость дерматоглифических показателей с показателями особенностей личности практически здоровых мужчин Украины. Из банка данных материалов научно-исследовательского центра Винницкого национального медицинского университета им. Н.И. Пирогова взяты первичные дерматоглифические показатели и данные анкет особенностей личности 92 практически здоровых мужчин в третьем поколении жителей Винницкой, Хмельницкой, части Тернопольской и Житомирской областей. Обработку дерматоглифов проводили по методике Cummins H. и Midlo Ch. (1961) в изложении Гладковой Т.Д. (1966). Для объективной оценки особенностей личности практически здоровых мужчин был определен ряд ведущих показателей, в состав которых отнесли целый ряд свойств темперамента (по Айзенку), тревожности (по Спилбергеру), акцентуированных черт личности (по Шмишеку), мотивационной направленности личности (по Роттерому), а также особенностей психоэмоциональной организации личности, агрессивности, уровня распространения астенических и депрессивных личностных проявлений (по цветовому тесту Люшера), которые определяли на основе использования личностных опросников и тестовых методик. Факторный анализ проведен в лицензионном пакете "Statistica 6.1". Определены главные факторы, которые свидетельствуют об ассоциированности особенностей личности практически здоровых мужчин с некоторыми дерматоглифическими показателями: "гребешковый счет пальцев кистей" (доля дисперсии - 13,22 %) и "величина угла atd" (доля дисперсии - 10,66 %). Анализ полученных взаимоотношений взаимозависимости показателей особенностей личности с дерматоглифическими показателями показал, что при увеличении показателей гребешковых счетов пальцев кистей и дельтового индекса степень вероятности роста показателей нейротизма по Айзенку, ситуативной и личностной тревожности по Спилбергеру, акцентуации характера эмотивного и возбуждающего типов по Шмишеку, субъективного контроля в области здоровья и болезни по Роттеру, черного и серого цвета по Люшеру уменьшается, а показателей акцентуации характера тревожного и демонстративного типов по Шмишеку, общей интернальности уровня субъективного контроля и в области учебных (профессиональных) отношений по Роттеру, синего и сине-зеленого цвета по Люшеру - увеличивается. При увеличении величины угла atd на обоих ладонях степень вероятности роста показателей нейротизма по Айзенку, ситуативной и личностной тревожности по Спилбергеру, акцентуации характера эмотивного, тревожного и возбуждающего типов по Шмишеку, синего цвета по Люшеру увеличивается, а показателей акцентуации характера демонстративного типа по Шмишеку, общей интернальности уровня субъективного контроля, в области учебных (профессиональных) отношений и в области здоровья и болезни по Роттеру, сине-зеленого, черного и серого цвета по Люшеру - уменьшается. Применение факторного анализа позволило определить наиболее значимые взаимосвязи показателей особенностей личности с дерматоглифическими показателями.*

Ключевые слова: *дерматоглифические показатели, показатели особенностей личности, практически здоровые мужчины, факторный анализ.*

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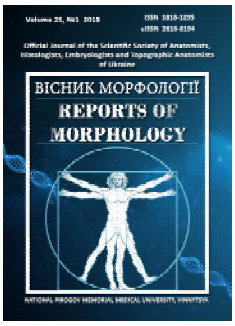

Morphofunctional changes in the lymphoid component of the rats prostate gland in conditions of immunostimulation

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To date, the state of the local immune system of the human prostate gland is not sufficiently studied, which prevents in-depth study of sexual disorders and infertility in men, as well as its common diseases: hypertrophy, adenoma, cancer. In order to study the morphological state of the lymphoid apparatus of the prostate of rats on the background of immunostimulation, 60 rat prostate glands were studied by histological, morphometric and statistical methods. Using the methods of variation statistics, we assessed the correctness of the distribution of signs for each of the obtained variation series, the average values for each attribute that was studied, standard errors and standard deviations. The reliability of differences in values between independent micrometric values with a normal distribution of signs was determined by the Student's criterion. The paper describes the patterns of formation of the local immune system of the prostate gland in the experiment after the introduction of immunoglobulin in adult male rats Wistar line. It was revealed that in rats after administration of immunoglobulin, the formation of lymphoid structures was observed three days earlier than in intact and control rats. First appear lymphoid formations in the stroma of the prostate gland, in the blood vessels - perivascular lymphoid nodules. By the end of the first week, lymphoid structures are formed in the glandular epithelium of the prostate gland - lymphoepithelial nodules. In lymphoid structures, the content of lymphocytes in all periods exceeds the benchmarks with the maximum changes on day 7 of the study. Reactive changes in the capillary endothelium in close relationship with the restructuring of lymphoid nodules during antigenic stimulation indicate that they are redundant in providing immune homeostasis. Thus, against the background of immunostimulation, changes occur in the local immune system of the prostate gland, manifested in an increase in the number of immunocompetent cells, the formation of lymphoid nodules, and are accompanied by corresponding changes in the hemomicrocirculatory bed.

Key words: *prostate gland, immunostimulation, lymphoid component.*

Introduction

Functional and morphological features of the human prostate gland are an important problem in connection with the spread of its diseases, in the pathogenesis of which there are violations of specific and nonspecific mechanisms of protection [1, 4, 6, 7, 8, 26]. Lack of knowledge about the morphofunctional changes of the prostate gland and virtually no studies aimed at studying the morphological substrate of local nonspecific immune responses, prevents in-depth study of sexual disorders and infertility in men, as well as its common diseases: hypertrophy, adenomas, cancer [13, 17, 25, 29].

Existing data do not allow us to formulate the general patterns of prostate morphogenesis and to determine the role of its lymphoid formations in the formation of nonspecific and specific mechanisms of protection in the norm and pathology [2, 3, 5, 9, 10, 11, 12].

So we took for a purpose to investigate the morphological condition of the rat prostate lymphoid apparatus on the background of immunostimulation.

Materials and methods

As objects of the study, 60 prostate glands of sexually mature male rats (obtained from the vivarium of the Institute of Pharmacology and Toxicology, Academy of Medical Sciences of Ukraine, Kyiv) weighing 220-240 g (age 5-6 months) were taken.

The experimental animals were divided into three groups: the first group was intact animals (10 rats), the second group was experimental (40 rats), and the third group was control (10 rats). The three groups were in the same conditions. The research followed international rules and principles of the "European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 1986) and the "General Ethical Principles of Animal Experiments" (Kyiv, 2001) and Law of Ukraine №3447 "On the Protection of Animals from Cruelty" - IV dated 21.02.2006.

Experimental animals were intramuscularly injected with human normal immunoglobulin at a dose of 1 mg. Immunoglobulin is characterized by high antigenic activity and no toxic, pyrogenic, adjuvant effect. Controls were rats administered saline at equivalent doses. Given the presence of circadian rhythms in the lymphoid organs, slaughter of rats was performed at the same time of day. Euthanasia of rats was performed with an overdose of thiopental anesthesia on 3, 7, 14, 21 days with the observance of the "Rules for working with experimental animals".

Serial paraffin sections, 5-6 μm thick, stained with hematoxylin and eosin, were prepared for the study. The sections after staining were enclosed in polystyrene under the coverslip and examined in a light microscope. Morphological examination of the obtained sections was performed using an Olimpus microscope "PrimoStar" FL "ILED" with digital microphotography using Olimpus Soft (2011).

Among the elements of the lymphoid tissue of the prostate, the average number of immunocompetent cells was calculated: lymphocytes, plasmocytes, macrophages.

Quantitative analysis of the results of the morphometric study and statistical processing of the morphometric data were performed according to conventional statistical methods and using the programs "Microsoft Office Excel" and "Statistica 6.1". Using the methods of variational statistics, the correctness of the distribution of traits by each of the variations obtained, the average values for each trait studied, standard errors and standard deviations were evaluated. The significance of the difference of values between independent micrometric values in the normal distribution of features was determined by a paired two tailed Student's test.

Results

The prostate gland of rats is represented by a complex of glandular formations: ventral, dorsal lobes and coagulation glands, the dimensions of which are 10-12 x 7-9 mm, 6-8 x 5-6 mm, 8-12 x 4-6 mm. The parenchyma of the organ consists of the alveolar-tubular glands, the epithelium of which is represented by secretory and basal cells.

The formation of lymphoid clusters occurred through the migration of lymphocytes from the blood vessels. Lymphoid clusters consisted of small and medium lymphocytes, 60-70% of which belong to thymus-dependent lymphocytes.

The composition of lymphoid clusters varied from 4 to 7 days after the experiment. Reticular cells, macrophages, and plasma cells appeared among the lymphoid cells. Detected lymphoblasts with figures of mitosis in the nuclei. Due to the proliferation of lymphoid cells, perivascular lymphoid nodules developed on the basis of lymphoid clusters (Fig. 1). Intramuscular administration of antigen near the blood vessels and prostate gland area increased the number of lymphoid formations.

From the beginning of the experiment, the number of lymphoid formations associated with blood vessels decreased with the increase of its term, and in the area of the glandular epithelium increased. The cellular composition of lymphoid formations after the introduction of gamma-globulin changed most sharply at 3-7 days (Table 1).

As a result of antigenic stimulation on the third day increased migration of lymphocytes. Lymphocytes, for the most part, were located diffusely under the glandular epithelium in the experimental group, and single lymphocytes were observed in similar places in animals of control group. At this time, the number of blast cell forms of lymphocytes increased markedly (compared to the control group). Macrophage contacts with lymphocytes are monitored. The cells form figures in the form of sockets, in the center of which there is a macrophage, and around it there are lymphocytes.

The preferred site of blast localization for the third day after immunization is lymphoid clusters near the blood vessels. In these areas blasts form clusters of 5-6 cells in the field of view, in the control group of animals, these cells are virtually undetermined. The presence of macrophages and close contacts with them precursors of plasma cells indicate that the interaction of macrophages and lymphocytes is necessary not only at the time of initiation of immune response.

The formation of reproductive centers in the lymph nodes of the prostate of rats begins after 3-5 days after immunization, subsequently in them the proliferation of cells occurs, which leads to an increase in the size of the

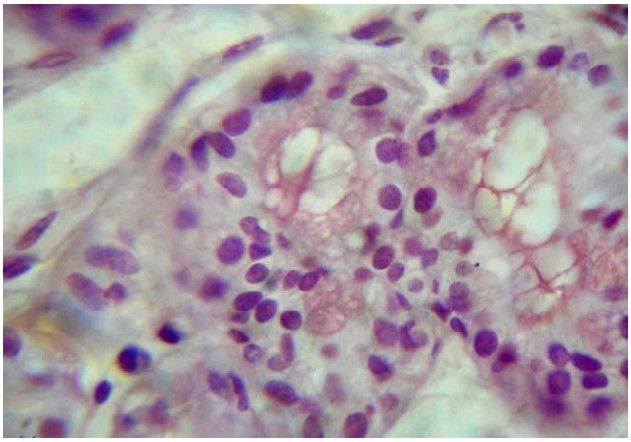

Fig. 1. Prostate gland of a mature rat for 7 days after immunization. Hematoxylin-eosin. x600.

Table 1. Percentage ratio (X±Sx) of cells in rats prostate lymphoepithelial nodules after single administration of gamma globulin.

Cells	Control group	Day of experiment			
		3	7	14	21
Small lymphocytes	32.05±3.05	18.03±3.05	14.07±1.02	12.04±2.05	12.01±1.02*
Medium lymphocytes	59.02±6.01	66.00±4.02	66.05±5.02	69.01±3.06	70.04±4.06*
Lymphoblasts	6.024±1.022	9.045±0.501	10.2±0.48	12.03±0.50	10.06±0.72*
Plasmocytes	2.062±0.506	4.026±0.501	6.035±0.305	6.036±0.245	7.066±0.201*
Macrophages	1.027±0.308	3.066±0.203	3.045±0.208	1.022±0.102	1.045±0.201*

Notes: * - $p<0.05$ compared to control.

reproductive center and the formation of other zones of lymphoid structures. Changes in the cellular composition of perivascular lymphoid nodules after antigenic stimulation are largely similar to those in lymphoepithelial nodes.

On the seventh day after antigenic exposure in the lymphoepithelial nodules in the subepithelial zone was observed increased migration of lymphocytes to the epithelium, which is represented by different cell forms and can be attributed to the stratified cuboidal epithelium. In lymphoepithelial nodes, in addition to this zone, there are 2 more zones. Darker is the peripheral area, which consists of tightly adjacent small lymphocytes. This zone in the form of a "hat" covers the central zone.

It should be noted the different nature of the processes that occur at 5-7 days in the reproduction centers after antigenic stimulation. In the latter there is a fairly homogeneous picture: blasts predominate in the dark zone (and it is the origin of the breeding center). Some of them are mitotically divided.

Due to proliferation, lymphoid structures spread towards the glandular epithelium. The content of reticular cells and lymphoblasts increased, and plasma cells appeared. A large number of macrophages are observed on the seventh day after immunization in reproduction centers, where plasmablasts and young plasmocytes are in close relationship with macrophages.

By the end of the second week (on the 14th day), all the zones were clearly visible in the lymph nodes. In the central area of the lymphoepithelial nodules, the highest number of mitoses was observed. In the peripheral zone, the content of plasma cells and small lymphocytes increased. In the subepithelial zone, the number of phagocytic macrophages increased in the cytoplasm which contained the remains of lymphocyte nuclei. These cells were surrounded by lymphocytes, reminiscent of immune sockets described in immunological studies. In the subepithelial area, compared to the control, the percentage of small lymphocytes increased, and the average lymphocytes decreased, reticular cells appeared, the number of macrophages increased.

On the twenty-first day with the introduction of normal doses of antigen, the structure and cellular composition of lymphoid structures differed little from the controls. In some lymph nodes, the reproduction centers subjected to reverse development. Destructive changes were detected in individual lymphocytes.

The lumen of the lymphatic vessels and venules was filled with small lymphocytes. After antigenic stimulation in the early stages of the experiment, on the 2-4 days was determined the expansion of the inter-endothelial contacts of the blood capillaries of the lymphoepithelial nodes. Near the apical edge of the endothelial cells, cracks were found, the localization of which apparently corresponded to the loci of increased permeability. Of particular importance in the barrier function of the prostate gland are the blood vessels located near the lymphoid formations and in the stroma of the prostate gland. The change in cellular composition in the lymphoid nodules of the rat prostate after antigenic stimulation causes specific cytoarchitectonics of the hemomicrocirculatory bed. It is established that the area occupied by different links of the microcirculatory bed of lymph nodes increases with antigen loading. The lumen of the blood capillaries increases and migration through the capillaries and postcapillary venules of lymphocytes and plasma cells increases.

Specific changes in the capillary wall, along with the reticular cells of the lymph nodes of the prostate, play an important role in the cell rearrangement of lymphoid structures and the formation of their specific microenvironment. Reactive changes in capillary endothelium in close relationship with the restructuring of lymphoid nodules during antigenic stimulation indicate their reserve capacity for immune homeostasis.

During antigenic load venules also undergo certain changes. The wall of venules is lined by endothelium, whose morphology varies depending on the phase of the immune response. In the early stages, when there is an increased influx of lymphocytes to the lymph nodes, endothelial cells are hypertrophied, take the form of prismatic epithelium, and lymphocytes through the wall of venules are evicted into the surrounding tissue. Sometimes venules acquire the character of post-capillary venules with high endothelium. In the early stages of the immune response, the number of macrophages and lymphocytes increases, neutrophil and eosinophil granulocytes appear. At the height of the immune response there are many cells of the plasma row at different stages of maturation, macrophages with phagocytosed cellular elements in the venules. The increase in the area occupied by the various units of the microcirculatory bed

indicates an increase in intercellular and intracellular transport of substances.

Discussion

Therefore, we assume that the revealed topographic proximity of lymphoid formations with glands at the level of excretory ducts is due to the protective role of lymphocytes in cases of antigens penetration at this site, and close microtopographic relations with the terminal divisions provides one of the mechanisms of immune responses - products of immune responses, which are then included in the secretion of the glands, which has been proven in several works [14, 15, 16, 18]. Considering the changes in the local immune system of the prostate, one cannot ignore the large individual variability in the amount of lymphoid tissue in it. Such a picture can be due to different lifestyles, different antigenic effects of the environment, different reactivity of the body. More significant range of fluctuations from the minimum to the maximum numbers is usually observed during the period of greatest development of lymphoid tissue, the formation of nodules in it.

For lymphoid tumors of the prostate, the structures of the microenvironment are the glandular epithelium, the components of the reticular tissue and the cells of the walls of the microvessels. The formation and glandular epithelium, development and transformation of the microcirculatory bed units are closely related and interdependent with the reaction of the perivascular connective and reticular tissue, with the formation of its cellular and fibrous structures [19, 20, 22].

Considering the lymphoid structures of the prostate as a morpho system, that is, a complex of structurally and functionally interconnected elements that form a single integral system, we can distinguish the basic patterns of their morphogenesis.

First, the development of lymphoid structures in the prostate occurs under the influence of natural antigenic stimulation in pre- and post-natal ontogeny.

Second, the formation of lymphoid structures is closely linked to the level of development, both in the glandular epithelium and in the stroma of the prostate and reticular components of the stroma and vascular system in it.

Third, the development of lymphoid structures of the prostate has a stage character and is determined by interstitial and intercellular interactions.

In our opinion, we can distinguish the following stages of development of lymphoid structures of the prostate:

- during the first stage loose clumps of lymphoid cells are formed. In this area of the connective tissue of the prostate, histochemical changes are associated with the formation of the stroma of the lymphoid clusters, and its own vascular bed begins to form. These processes play an important role in the preparation of microenvironment;

- the second stage is characterized by a gradual increase in the number of lymphocytes and cells of the monocyte row, their diffuse distribution, the appearance of mitotic activity. The vascular bed of lymphoid nodules is being differentiated, in which, in addition to capillaries, arterial and venular vessels appear. In the venular branch, there are specialized areas with high endothelium required for lymphocyte recycling. Occur further changes in the stroma associated with an increase in reticular fibers and the formation of a thin capsule;

- in the third stage, the processes of genesis of lymphoid nodules are stabilized, which is manifested by the absence of pronounced morphological changes;

- the fourth stage is characterized by the reverse development of the lymph nodes of the prostate and involutive processes in them, typical for the organs of the immune system.

Thus, we first discovered the features of the structure of lymphoid prostate formation, which are expressed in the high saturation of all prostate structures diffusely located lymphoid cells and lymphoid nodules of different sizes and stages of development, which have a peculiar organization and are in close relationship with the epithelial and stromal structures of the prostate.

Analysis of the data on the morphogenesis of the lymphoid structures of the prostate indicates that they develop as peripheral organs of the immune system and participate in both local and general immune reactions. Carrying out a detailed study of the development of lymphoid structures of the prostate of rats in normal and after exposure to the antigen, due to the need to confirm the characteristics of the organization and function of the lymphoid formations of the prostate of a human, revealed by them, their connection with histogenetic processes in the prostate, as well as to determine the genesis factors of lymphoid apparatus prostate [21, 24, 27].

Therefore, we first obtained data on the formation of a local prostate immune system in an experiment after intramuscular injection of immunoglobulin into mature Wistar rats. In rats, after intramuscular administration, immunoglobulin formation was observed to occur three days earlier than intact and control rats. Lymphoid formations initially appear in the stroma of the prostate gland, near the blood vessels - perivascular lymph nodes. By the end of the first week, the formation of lymphoid structures in the area of the glandular epithelium of the prostate - lymphoepithelial nodes appears. In lymphoid structures, the content of lymphocytes in all periods exceeds the control values.

The work carried out is the basis for the development of a new direction for the further study of age-related changes in the cellular composition and histophysiology of prostate tissue, to create models of organ functioning in norm and pathology and to develop on this basis rational methods of correction of hormonal homeostasis, organ secretion and regulation of fertility. The results of this work open a new direction in the study of prostate morphogenesis in normal and experiment, in age and evolutionary aspects, which is important for the development of a modern understanding of the mechanisms of formation of the prostate tissue systems in ontogeny.

In the future it is planned to continue the study of morphogenesis of lymphoid structures of the prostate of rats by immunohistochemical studies.

Conclusions

1. Formation of the prostate's own lymphoid apparatus in rats occurs by the migration of lymphocytes from the blood vessels.

2. On the background of immunostimulation, the formation of lymphoid structures is noted three days earlier than in intact and control rats. Initially, lymphoid lesions appear in the stroma of the prostate gland, near blood vessels - the perivascular lymph nodes. By the end of the first week, lymphoid structures are forming in the prostate gland glandular epithelium.

3. In lymphoid structures of the prostate of experimental animals the content of lymphocytes in all periods exceeds the control values.

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МОРФОФУНКЦІОНАЛЬНІ ЗМІНИ ЛІМФОЇДНОГО КОМПОНЕНТА ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ЩУРІВ В УМОВАХ ІМУНОСТИМУЛЯЦІЇ

Євтушенко, В.М., Сирцов, В.К., Попко С.С.

На сьогоднішній день стан локальної імунної системи передміхурової залози людини є недостатньо дослідженим, що перешкоджає поглибленому вивченню статевих розладів і безпліддя у чоловіків, а також її поширених захворювань: гіпертрофії, аденоми, раку. Мета роботи - вивчити морфологічний стан лімфоїдного апарату передміхурової залози щурів на тлі імуностимуляції. За допомогою гістологічних, морфометричних та статистичних методів дослідження були вивчені 60 передміхурових залоз щурів. Оцінили правильність розподілу ознак за кожним із отриманих варіаційних рядів, середні значення за кожною вивченою ознакою, стандартні помилки та стандартні відхилення. Достовірність різниці значень між незалежними мікрометричними величинами при нормальному розподілі ознак визначали за критерієм Ст'юдента. В роботі охарактеризовані закономірності формування локальної імунної системи передміхурової залози в експерименті після внутрішньом'язового введення імуноглобуліну у статевозрілих щурів лінії Вістар. Виявлено, що у щурів після введення імуноглобуліну лімфоїдні структури формуються на три доби раніше, ніж у інтактних і контрольних тварин. Спочатку з'являються лімфоїдні утворення в стромі передміхурової залози, а біля кровоносних судин - периваскулярні лімфоїдні вузлики. До кінця першого тижня лімфоїдні структури формуються в області залозистого епітелію передміхурової залози - лімфоепітеліальних вузликів. У лімфоїдних структурах вміст лімфоцитів в усі періоди перевищує контрольні показники з максимальними змінами на 7 добу дослідження. Реактивні зміни ендотелію капілярів в тісному взаємозв'язку з перебудовою лімфоїдних вузликів при антигенній стимуляції вказують на їх резервні можливості у забезпеченні імунного гомеостазу. Таким чином, на тлі імуностимуляції відбуваються зміни в локальній імунній системі передміхурової залози, котрі проявляються у збільшенні кількості імунокомпетентних клітин, формуванні лімфоїдних вузликів, і супроводжуються відповідними змінами гемомікроциркуляторного русла.

Ключові слова: *передміхурова залоза, імуностимуляція, лімфоїдний компонент.*

МОРФОФУНКЦИОНАЛЬНЫЕ ИЗМЕНЕНИЯ ЛИМФОИДНОГО КОМПОНЕНТА ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ КРЫС В УСЛОВИЯХ ИММУНОСТИМУЛЯЦИИ

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На сегодняшний день состояние локальной иммунной системы предстательной железы человека исследовано недостаточно, что препятствует углубленному изучению половых расстройств и бесплодия у мужчин, а также ее распространенных заболеваний: гипертрофии, аденомы, рака. Цель работы - изучить морфологическое состояние лимфоидного аппарата предстательной железы крыс на фоне иммуностимуляции. С помощью гистологических, морфометрических и статистических методов исследования были изучены 60 предстательных желез крыс. Оценили правильность распределения признаков по каждому из полученных вариационных рядов, средние значения по каждому изученному признаку, стандартные ошибки и стандартные отклонения. Достоверность различий значений между независимыми микрометрическими величинами при нормальном распределении признаков определяли по критерию Стьюдента. В работе охарактеризованы закономерности формирования локальной иммунной системы предстательной железы в эксперименте после введения иммуноглобулина у половозрелых крыс линии Вистар. Выявлено, что у крыс после введения иммуноглобулина лимфоидные структуры формируются на трое суток раньше, чем у интактных и контрольных животных. Сначала появляются лимфоидные образования в строме предстательной железы, а возле кровеносных сосудов - периваскулярные лимфоидные узелки. К концу первой недели лимфоидные структуры формируются в области железистого эпителия предстательной железы - лимфоэпителиальных узелков. В лимфоидных структурах содержание лимфоцитов во все периоды превышает контрольные показателями с максимальными изменениями к 7 суткам исследования. Реактивные изменения эндотелия капилляров в тесной взаимосвязи с перестройкой лимфоидных узелков при антигенной стимуляции указывают на их резервные возможности в обеспечении иммунного гомеостаза. Таким образом, на фоне иммуностимуляции происходят изменения в локальной иммунной системе предстательной железы, проявляющиеся в увеличении количества иммунокомпетентных клеток, формировании лимфоидных узелков, и сопровождаются соответствующими изменениями гемомикроциркуляторного русла.

Ключевые слова: *предстательная железа, иммуностимуляция, лимфоидный компонент.*

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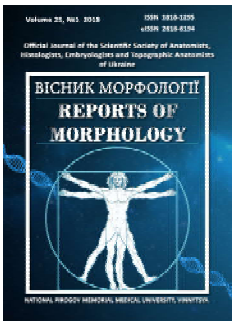

Features of the interaction of indicators of peculiarities of personality and characteristics of the quality of life of pupils and student youth by the cluster analysis

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Recently, while conducting scientific research in the field of theoretical and preventive medicine, biomedical preventive anthropology and statistical processing of their results, one of the leading places is the cluster analysis procedure, which involves the search for the patterns of grouping as research objects and their leading features in separate local plurals and subsets, that is, in separate clusters. Researches that provided for determining the leading characteristics of the quality of life and the peculiarities of the course of psychological adaptation processes based on the use of commonly accepted psychohygienic practice of personal questionnaires were conducted on the basis of educational institutions in Ivano-Frankivsk. Statistical analysis of the obtained data provided for the use of descriptive statistics and cluster analysis procedures using the licensed standardized application package of the multivariate statistical analysis "Statistica 6.1 for Windows" (license number BXXR901E245722FA). The results of the conducted research indicate the existence of an extremely stable structure of the identified groups, among which in all investigated cases, it necessary to note the cluster associated with the leading indicators of quality of life, which united in its structure characteristics of quality of life on the scales Bodily Pain (BP, Pain scale), Physical Functioning (PF, Physical Functioning scale), Mental Health (MH, Mental Health Scale), General Health (GH, General Health Scale), Vitality (VT, Viability Scale) and Social Functioning (SF, scale of social functioning), neuro-psychical cluster combining personal and situational anxiety, depressive and asthenic states, as well as an integral cluster that included in its structure the characteristics of quality of life on the scale of Role-Emotional (RE, role-playing role scale) and Role-Physical (RP, scale of role-physical functioning) and indicators of subjective control in health and disease and neuroticism. The obtained data should further find a proper place in the structure of diagnostic and preventive approaches to assess the state of health and functional state of the body of pupils and students.

Keywords: *pupils and students, modern institutions of education, quality of life, mental adaptation, interaction, cluster analysis.*

Introduction

Recently, while conducting scientific research in the field of theoretical and preventive medicine, biomedical preventive anthropology and statistical processing of their results, one of the leading places is occupied by cluster analysis procedures, which provide the search of grouping patterns as objects of research and their leading features in separate local sets and subsets, that is, into separate clusters [4, 17, 18, 19, 20, 22].

Indeed, a cluster is a group, a certain class, or a certain group of homogeneous units. Therefore, the main task of cluster analysis is to recognize the formation of homogeneous groups, classes, or associations in the multidimensional space of the studied features that are calculated [2, 8, 14, 15, 16].

The homogeneity of the collectively is determined by the rule of calculation of a certain metric, which characterizes

the degree of similarity of two separate units of the collectively. Such a metric can be the distance between them or the similarity factor. Units similar to the selected metrics define units as belonging to one type, ie as homogeneous. In this regard, the choice of metric is the nodal point of the cluster analysis, which determines the final variant of division of collectively into classes. Next, according to the features of the metric scale, a distance matrix with zero diagonal elements is formed, which is in fact the main information base of cluster analysis, with Euclidean and Manhattan distances being the most commonly used and popular metrics [3, 4, 5, 7, 9].

Therefore, cluster analysis as a modern method of multidimensional statistical analysis is designed to provide objective spatial classification of identical objects, characterized by the presence of a certain set of indicators, and their subsequent meaningful grouping in a certain structured space based on the use of either agglomerational-hierarchical or divisional-iteration approaches [1, 4, 6, 10].

Thus, the methods of cluster analysis are quite versatile, involve the use of various algorithms for mathematical transformations, determine the strict observance of the accuracy of statistical procedures, and, at the same time, have extremely great prospects for carrying out statistical procedures of multidimensional classification of the studied objects during the implementation of medical and biological research, including the study of the relationship between the criteria of mental adaptation (MA), which is the process of establishing optimal about the relationship between personality and environment in the course of performance of human activity and quality of life (QoL) characteristics, which is a certain generalized integral characteristic of the physical, psychological, emotional and social functioning of the human body, which reproduces its subjective perception of its somatic and mental state in direct relation to the actual state of health [11, 13, 21, 22, 23].

The *purpose* of the work is to establish the characteristics of the relationship between personality traits and characteristics of pupils and students youth according to the use of cluster analysis procedures.

Materials and methods

The research was conducted on the basis of a number of modern educational institutions in Ivano-Frankivsk, namely: school (boarding school) for gifted children from rural areas, professional lyceum of road transport and construction, music specialized school, financial-commercial cooperative college and Vasyl Stefanyk Precarpathian National University. During the performance of scientific work, 300 pupils and students were surveyed, 150 people each.

Performing comprehensive assessment of the characteristics of the course of MA in pupils and students led to the definition of such personality traits (PT), as the level of extraversion-introversion and neuroticism through the use of a personal questionnaire of Eysenck, the level of situational (SA) and personal (PA) anxiety - based on Spielberger's personal questionnaire, personality degree of expression of asthenic (AC) and depressive condition (DC) - during the use of personal questionnaire of Malkova and psychometric scale of Tsung, the level of expression of subjective control (LSC) through the use of a personal Rotter questionnaire [13].

Leading QoL indicators, which included data on the general health of pupils and students according to the scale General Health (GH), the level of physical functioning of the organism according to the scale Physical Functioning (PF), the degree of influence of physical condition on the features of role functioning according to the Role-Physical scale (RP), the level of influence of emotional state on the role functioning of students and students according to the Role-Emotional scale (RE), the intensity of painful sensations that occur, according to the scale of Bodily Pain (BP), the degree of expression of indicators of vitality in accordance with the sense of fullness of forces, energy and stability according to a scale of Vitality (VT), and features self-assessment scale for mental health according to Mental Health scale (MH), determined on the basis of the use of non-specific questionnaire QoL "SF-36 Health Status Survey" [11].

Finally, the prognostic evaluation of the results obtained in the previous stage of the scientific research involved the implementation of descriptive statistics and cluster analysis procedures based on the use of the licensed standardized statistical analysis software package "Statistica 6.1 for Windows" (license number BXXR901E245722FA).

Results

Considering the data obtained during the use of cluster analysis procedures among young women who studied at school, it was necessary to distinguish 3 leading clusters that characterized the features of the interconnections of the leading components of QoL and PT, namely: cluster № 1 (integral), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and the LSC indicators in health and disease and neuroticism, cluster № 2 (associated with leading QoL indicators), which combines the characteristics of QoL according to the Bodily Pain (BP), Physic al Functioning (PF), General Health (GH), Mental Health (MH), Social Functioning (SF) and Vitality (VT) scales, cluster № 3 (neuro-psychic), which included PA, SA, DC and AC indicators. Among the young women who studied at school, there were also 3 leading clusters, which characterized the features of the interconnections of the leading components QoL and PT, which included the cluster № 1 (integrated), which united in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and LSC indicators in health and disease and neuroticism, cluster № 2 (linked to the leading QoL indicators), combining QoL characteristics according to the Physical Functioning (PF), Bodily Pain (BP), Mental Health (MH), General Health

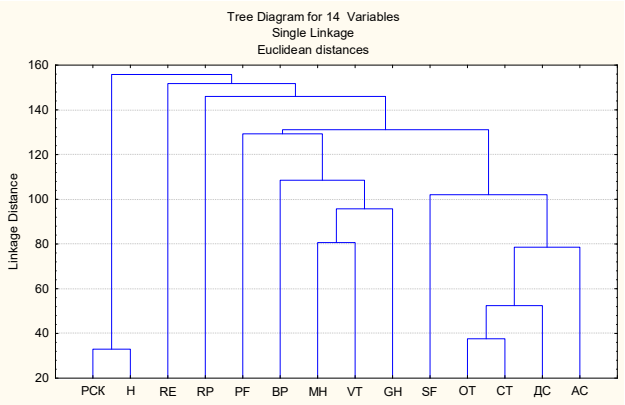

Fig. 1. Features of combining the main QoL and PT survey clusters studied among young men who studied in schools.

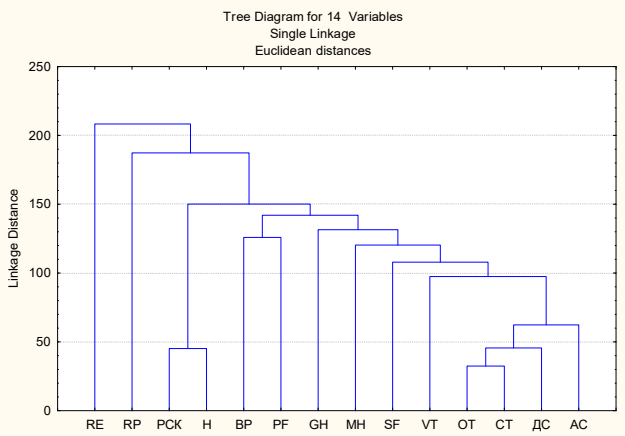

Fig. 2. Features of combining the main QoL and PT survey clusters studied among young women who studied in schools.

(GH), Vitality (VT) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included indicators PA, SA, DC and AC (Fig. 1-2).

In evaluating the results of the use of cluster analysis procedures among young women who studied under the conditions of professional lyceum, it was necessary to distinguish 3 leading clusters that characterized the features of the interconnections of the leading components of QoL and PT, namely: cluster № 1 (integral), which combined in its structure the characteristics of QoL according to the Role-Emotional (RE) and Role-Physical (RP) scales and the LSC indicators in the field of health and disease and neuroticism, cluster № 2 (associated with leading indicators QoL), which combined the QoL characteristics on the Bodily Pain (BP), Physical Functioning (PF), General Health (GH), Mental Health (MH), Social Functioning (SF) and Vitality (VT) scales, cluster № 3 (neuro-psychic), which included indicators PA, SA, DC and AC. Among the young men who studied under the conditions of professional lyceum, there were also 3 leading clusters, which characterized the features of the interconnections of the leading components QoL and PT, which included the cluster № 1 (integrated), which united in its QoL characteristics structure according to the Role-Emotional (RE) and Role-Physical (RP) scales and health and disease and neuroticism LSC indicators, cluster № 2 (associated with leading QoL indicators), combining QoL characteristics according to the Physical Functioning (PF), Bodily Pain (BP), Mental Health (MH), Vitality (VT), General Health (GH) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included PA, SA, DC and AC indicators (Fig. 3-4).

Analyzing the results obtained from the use of cluster analysis procedures among young women who studied in terms of specialized school, it was also necessary to distinguish 3 leading clusters that characterized the features of the interconnections of the leading components of QoL and PT, namely: cluster № 1 (integral), which combined in its structure QoL characteristics on the Role-Emotional (RE) and Role-Physical (RP) scales and the health and disease and neuroticism LSC indicators, cluster № 2 (linked with the leading QoL indicators), which combined QoL features according to Physical Functioning (PF), Bodily Pain (BP), Mental Health (MH), Vitality (VT), General Health (GH) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included indicators in its structure PA, SA, DC and AC. At the same time, the following three clusters, which

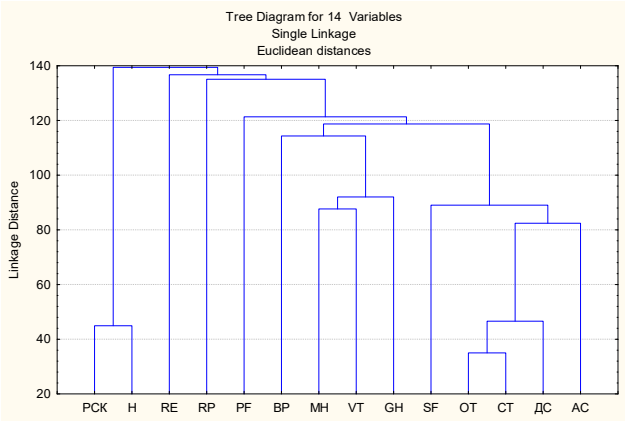

Fig. 3. Features of combining the main QoL and PT survey clusters studied among young men who studied in lyceum.

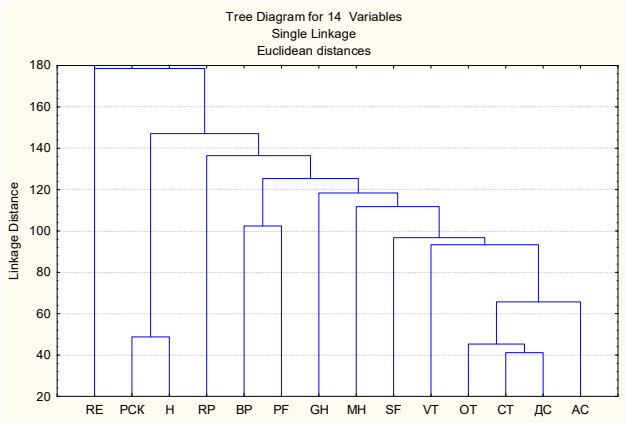

Fig. 4. Features of combining the main QoL and PT survey clusters studied among young women who studied in lyceum.

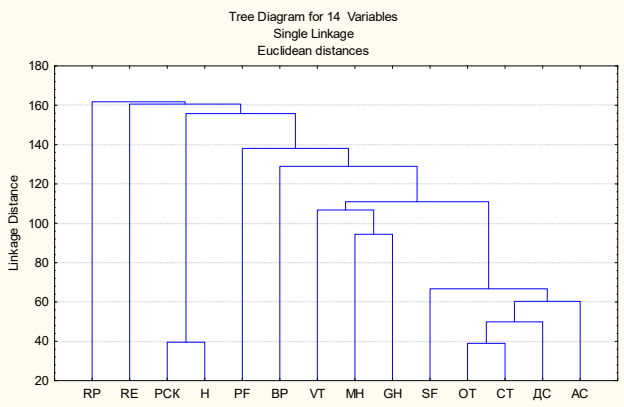

Fig. 5. Features of combining the main QoL and PT survey clusters studied among young men who studied in specialized school.

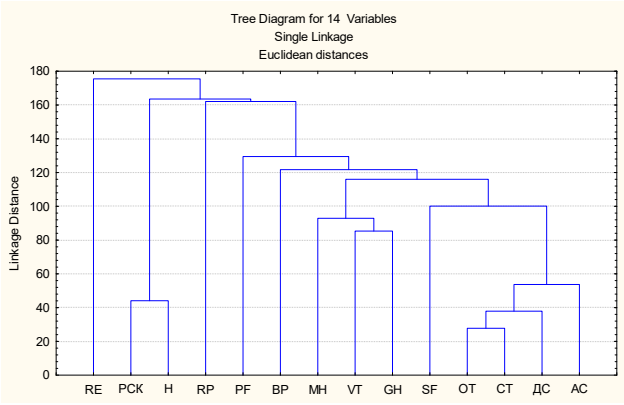

Fig. 6. Features of combining the main QoL and PT survey clusters studied among young women who studied in specialized school.

characterized the features of the interconnections of the leading QoL and PT components which included cluster № 1 (integral), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and the health and illness and neuroticism LSC indicators, cluster № 2 (linked to leading QoLs indicators) that combines QoL characteristics according to the Physical Functioning (PF), Bodily Pain (BP), Vitality (VT), Mental Health (MH), General Health (GH) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included the indicators PA, SA, DC and AC (Fig. 5-6).

Considering the data obtained during the use of cluster analysis procedures among college young women, it was necessary to distinguish 3 leading clusters that characterized the features of the intrasystem connections of the leading components of QoL and PT, namely: cluster № 1 (integral), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and the LSC indicators in health and disease and neuroticism, cluster № 2 (associated with leading QoL indicators), which combined the characteristics of QoL according to the Bodily Pain (BP), Physical Functioning (PF), General Health (GH), Mental Health (MH), Vitality (VT) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included PA, SA, DC and AC indicators.

Among the young men who studied in college, there were also three leading clusters that characterized the features of the interconnections of the leading QoL and PT components, which included the cluster № 1 (integrated), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and LSC indicators in health and disease and neuroticism, cluster № 2 (linked to the leading QoL indicators), combining QoL characteristics according to Physical Functioning (PF), Bodily Pain (BP), Vitality (VT), Mental Health (MH), General Health (GH), Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included indicators of PA, SA, DC and AC in its structure (Fig. 7-8).

Finally, in evaluating the results of the use of cluster analysis procedures among university young women, it was necessary to identify 3 leading clusters that characterized the intrinsic relationships of the leading components of QoL and PT, namely: cluster № 1 (integral), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and the LSC indicators in health and disease and neuroticism, cluster № 2 (associated with leading QoL indicators), which combined the characteristics of QoL according to the Bodily

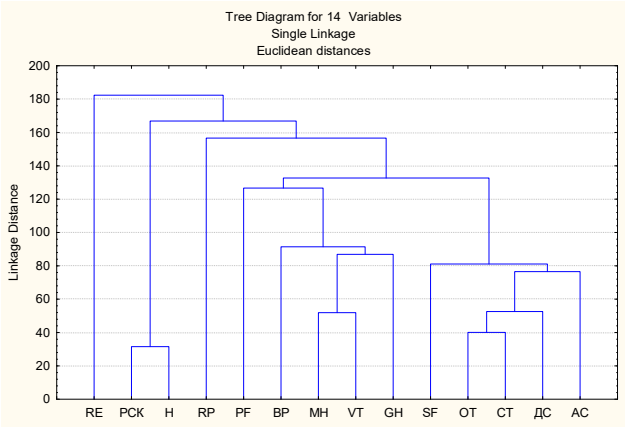

Fig. 7. Features of combining the main QoL and PT survey clusters studied among young men who studied in college.

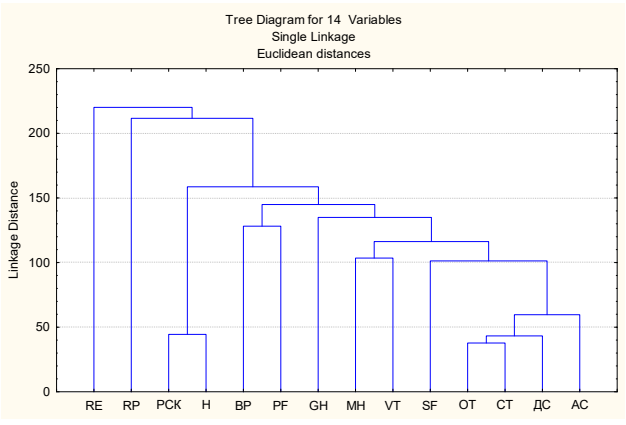

Fig. 8. Features of combining the main QoL and PT survey clusters studied among young women who studied in college.

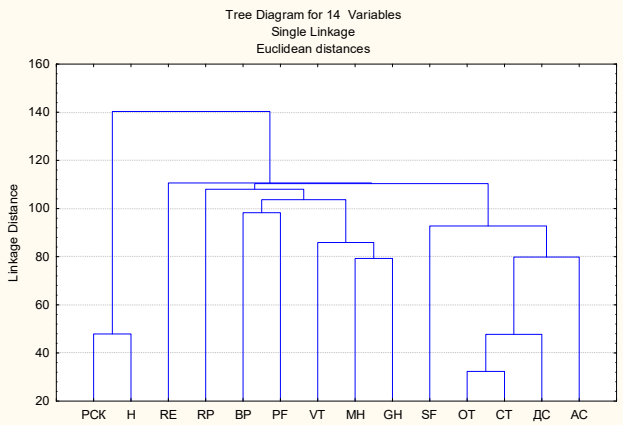

Fig. 9. Features of combining the main QoL and PT survey clusters studied among young men who studied in university.

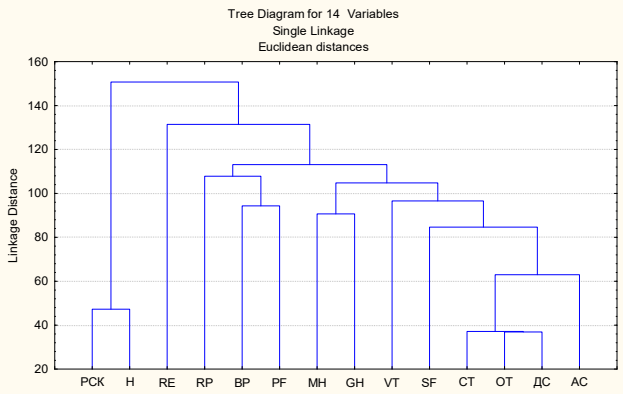

Fig. 10. Features of combining the main QoL and PT survey clusters studied among young women who studied in university.

Pain (BP), Physical Functioning (PF), Mental Health (MH), General Health (GH), Vitality (VT) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included in its structure PA, SA, DC and AC indicators. Among the young men who studied at the university, there were also three leading clusters that characterized the features of the interconnections of the leading components QoL and PT, which included the cluster № 1 (integrated), which combined in its structure QoL characteristics according to the Role-Emotional (RE) and Role-Physical (RP) scales and LSC indicators in health and disease and neuroticism, cluster № 2 (linked to the leading QoL indicators), which combined QoL characteristics according to the Bodily Pain (BP), Physical Functioning (PF), Vitality (VT), Mental Health (MH), General Health (GH) and Social Functioning (SF) scales, cluster № 3 (neuro-psychic), which included indicators PA, SA, DC and AC (Fig. 9-10).

Discussion

Research data based on the use of cluster analysis procedures indicate that this approach is an extremely powerful tool for establishing any, but above all, functional relationships between the organism's adaptive resources and objective and subjective characteristics of health status.

In this context, it should be noted that this approach significantly expands and supplements the data presented in a number of studies published in recent years [12, 17, 18, 19, 20, 21, 22]. And, to be noted separately, determine the perspective of consideration in the development of modern diagnostic (development of methods of complex assessment of the state of adaptation resources of the body of young men and young women) and preventive (introduction of effective health-saving technologies and measures of psychophysiological impact on the body and psycho-hygienic changes in the body state of the body) approaches to the assessment of the state of health and functional state of the body of pupils and students QoL concept [11, 13, 21, 22, 23].

In general, it should be emphasized that the data obtained were marked by the presence of extremely stable results and, consequently, the structures of the identified groups, among which in all the investigated cases it was necessary to note a cluster related to the leading QoL indicators, which united in its structure the QoL characteristics by Bodily Pain (BP, Pain Scale), Physical Functioning (PF, Scale Of Physical Functioning), Mental Health (MH, Mental Health Scale), General Health (GH, General Health Scale), Vitality (VT, Vitality Scale) and Social Functioning (SF, Scale Of Social Functioning) scales, a neuro-psychic cluster that combines PA, SA, DC, and AC indicators, as well as an integrated cluster that included in its structure QoL characteristics according to the Role-Emotional (RE, Role-Emotional Function Scale) and Role-Physical (RP, Role of Physical Functioning Scale) scales and LSC indicators in health and illness and neuroticism.

Conclusions

1. The results of the studies show that there is an extremely stable structure of the identified groups, among which in all the cases studied, it was necessary to note a cluster associated with leading indicators of quality of life, which combined in its structure the characteristics of quality of life according to the scale of Bodily Pain (BP, Scale of Pain), Physical Functioning (PF, Scale of Physical Functioning), Mental Health (MH, Mental Health Scale), General Health (GH, General Vitality Scale), Vitality (VT, Vitality Scale), and Social Functioning (SF, social functioning scale), neuro-psychic cluster, combining indicators of personal and situational anxiety, depressive and asthenic states, as well as an integral cluster that included in its structure characteristics of quality of life according to the Role-Emotional (RE, Scale of Role Emotional Functioning) and Role-Physical scales (RP, Role Scale of Physical Functioning) and indicators of subjective control in health and illness and neuroticism.

2. The obtained data should further find a place in the structure of diagnostic (development of methods of complex assessment of the state of adaptation resources of the body of young men and young women) and preventive (introduction of effective health-saving technologies and

measures of psychophysiological influence on the organism and psycho-hygienic correction of existing changes in the functional organism state) approaches to the assessment of the state of health and functional state of the body of pupils and students.

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ОСОБЛИВОСТІ ВЗАЄМОЗВ'ЯЗКУ ПОКАЗНИКІВ ОСОБЛИВОСТЕЙ ОСОБИСТОСТІ ТА ХАРАКТЕРИСТИК ЯКОСТІ ЖИТТЯ УЧНІВСЬКОЇ І СТУДЕНТСЬКОЇ МОЛОДІ ЗА ДАНИМИ КЛАСТЕРНОГО АНАЛІЗУ

Гжегоцький М. Р., Тимощук О. В., Черкасов В. Г., Дмитренко С. В., Шаповал О. М.

Останнім часом під час проведення наукових досліджень в галузі теоретичної і профілактичної медицини, біомедичної профілактичної антропології та статистичного опрацювання їх результатів, одне з провідних місць займають процедури кластерного аналізу, що передбачають пошук закономірностей групування як об'єктів дослідження, так і їх провідних ознак в окремі локальні множини та підмножини, тобто в окремі кластери. Дослідження, що передбачало визначення провідних характеристик якості життя та особливостей перебігу процесів психічної адаптації на підставі використання загальноприйнятих у психогігієнічній практиці особистісних опитувальників, проводили на базі освітніх закладів м. Івано-Франківська. Статистичний аналіз отриманих даних обумовлював використання процедур описової статистики та кластерного аналізу із застосуванням ліцензійного стандартизованого пакету прикладних програм багатовимірного статистичного аналізу "Statistica 6.1 for Windows" (ліцензійний № BXXR901E245722FA). Результати проведених досліджень засвідчують наявність надзвичайно стабільної структури виявлених угруповань, серед яких у всіх досліджуваних випадках необхідно відзначити кластер, пов'язаний із провідними показниками якості життя, що об'єднував у своїй структурі характеристики якості життя за шкалами Bodily Pain (BP, шкала болю), Physical Functioning (PF, шкала фізичного функціонування), Mental Health (MH, шкала психічного здоров'я), General Health (GH, шкала загального здоров'я), Vitality (VT, шкала життєздатності) і Social Functioning (SF, шкала соціального функціонування), нервово-психічний кластер, що поєднував у собі показники особистісної і ситуативної тривожності, депресивного і астенічного станів, а також інтегральний кластер, що включав у свою структуру характеристики якості життя за шкалами Role-Emotional (RE, шкала рольового емоційного функціонування) і Role-Physical (RP, шкала рольового фізичного функціонування) та показники рівня суб'єктивного контролю у галузі здоров'я і хвороби та нейротизму. Отримані дані мають у подальшому знайти належне місце в структурі діагностичних та профілактичних підходів до оцінки стану здоров'я та функціонального стану організму учнівської і студентської молоді.

Ключові слова: *учні і студенти, сучасні заклади освіти, якість життя, психічна адаптація, взаємозв'язок, кластерний аналіз.*

ОСОБЕННОСТИ ВЗАИМОСВЯЗИ ПОКАЗАТЕЛЕЙ ЛИЧНОСТНЫХ ОСОБЕННОСТЕЙ И ХАРАКТЕРИСТИК КАЧЕСТВА ЖИЗНИ УЧЕНИЧЕСКОЙ И СТУДЕНЧЕСКОЙ МОЛОДЕЖИ В СООТВЕТСТВИИ С ДАННЫМИ КЛАСТЕРНОГО АНАЛИЗА

Гжегоцкий М. Р., Тимощук О. В., Черкасов В. Г., Дмитренко С. В., Шаповал Е. Н.

В последнее время в ходе проведения научных исследований в области теоретической и профилактической медицины, биомедицинской профилактической антропологии и статистической обработки их результатов, одно из ведущих мест занимают процедуры кластерного анализа, предусматривающие поиск закономерностей группировки как объектов исследования, так и их ведущих признаков в отдельные локальные множества и подмножества, то есть в отдельные кластеры. Исследования, предусматривающие определение ведущих характеристик качества жизни и особенностей течения процессов психической адаптации на основе использования общепринятых в психогигиенической практике личностных опросников, проводились на базе образовательных заведений г. Ивано-Франковск. Статистический анализ полученных данных предусматривал использование процедур описательной статистики и кластерного анализа с применением лицензионного стандартизированного пакета прикладных программ многомерного статистического анализа "Statistica 6.1 for Windows" (лицензионный № BXXR901E245722FA). Результаты проведенных исследований свидетельствуют о наличии чрезвычайно стабильной структуры выявленных группировок, среди которых во всех исследуемых случаях необходимо выделить кластер, связанный с ведущими показателями качества жизни, объединяющий в своей структуре характеристики качества жизни по шкалам Bodily Pain (BP, шкала боли), Physical Functioning (PF, шкала физического функционирования), Mental Health (MH, шкала психического здоровья), General Health (GH, шкала общего здоровья), Vitality (VT, шкала жизнеспособности) и Social Functioning (SF, шкала социального функционирования), нервно-психический кластер, сочетающий в своей структуре показатели личностной и ситуативной тревожности, депрессивного и астенического состояний, а также интегральный кластер, включающий в свою структуру характеристики качества жизни по шкалам Role-Emotional (RE, шкала ролевого эмоционального функционирования) и Role-Physical (RP, шкала ролевого физического функционирования) и показатели уровня субъективного контроля в области здоровья и болезни, а также нейротизма. Полученные данные в дальнейшем должны найти надлежащее место в структуре диагностических и профилактических подходов к оценке состояния здоровья и функционального состояния организма ученической и студенческой молодежи.

Ключевые слова: *учащиеся и студенты, современные учреждения образования, качество жизни, психическая адаптация, взаимосвязь, кластерный анализ.*

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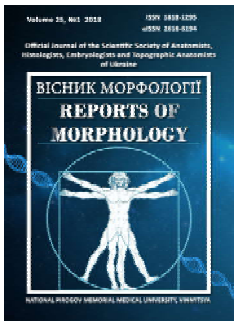

Features of the structural and functional parameters of the liver in experimental steatohepatitis and its correction in obese rats

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Summary. The improvement of the pharmacological strategy of non-alcoholic fatty liver disease is based on the study of the effect of pharmaceutical preparations on the structure and function of the liver. The pathogenesis of steatohepatitis is complex and multifactorial, mainly involving genetic, metabolic and environmental factors. The purpose of the study was to characterize the structural and functional parameters of the liver when using the biologically active compound Angiolin for the correction of experimental steatohepatitis. An experimental study was performed on 110 sexually mature white male rats weighing 180-220 grams, which were kept on a standard diet of vivarium. All animals were divided into two groups: control (30 intact animals) and experimental (80 animals). A model of non-alcoholic steatohepatitis was created for all animals of the experimental group. They were kept on a hypercaloric diet with a high fat and high cholesterol content for 8 weeks. After that, part of the animals (10 rats) was withdrawn from the experiment by intrapleural administration of sodium thiopental (50 mg/kg) and the necessary biochemical and morphological studies were performed. Part of the animals (30 rats) was continued to be kept on a high-fat diet for 4 weeks and the biologically active compound Angiolin was administered (20 rats), and Rings-Locke solutions were administered to 10 rats. After the creation of the model, the other animals of the experimental group (40 rats) were transferred to a full-fledged standard semi-synthetic starch-casein diet, and the biologically active compound Angiolin was administered for 20 rats and Ringer-Locke solution for another 20 rats for 4 weeks. Macroscopic evaluation and description of the liver of animals was carried out after withdrawal under thiopental anesthesia. Statistical analysis of the results was carried out using the program "STATISTICA 8" using parametric and non-parametric methods for assessing the results. It was found that the use of the biologically active compound Angiolin once a day for 30 days can reduce cytolysis syndrome (reduce biochemical parameters such as ALT, AST, gamma-glutamyl transpeptidase), reduce cholestasis syndrome (decrease in alkaline phosphatase level), and normalize liver function, improves the morphological state of hepatocytes, which indicates the normalization of the structural and functional state of the liver.
Key words: *liver disease, steatohepatitis, modelling, morphology, correction.*

Introduction

In recent years, the global burden of obesity and diabetes has led to a parallel increase in other metabolic complications, such as non-alcoholic fatty liver disease (NAFLD). NAFLD is the most common type of chronic liver injury in many countries [8, 17]. NAFLD includes a spectrum of syndromes ranging from simple steatosis, nonalcoholic steatohepatitis to fibrosis, cirrhosis and hepatocellular carcinoma [27]. The overall prevalence of NAFLD is 15-40% in Western countries and 9-40% in Asian populations. Over the last 15 years, NAFLD has grown dramatically in parallel with two major epidemics worldwide - obesity and type 2 diabetes [9]. Mortality in patients with NAFLD is significantly higher than in a similar age population [14]. Simple steatosis tends to be stable, but steatohepatitis can progress to cirrhosis [10]. The World Gastroenterology Organization (WGO) has recently published a number of comprehensive guidelines for the evaluation and treatment of NAFLD [13], with an emphasis on the distinction between simple steatosis and non-alcoholic steatohepatitis (NASH). Ukrainian scientists have established that the course of

nonalcoholic steatohepatitis with secondary arterial hypertension is characterized by higher histological activity, which leads to the progression of fibrotic changes [11].

In the last decade of the 20th century, the theory of "two hits" was the most proven theory of NASH pathogenesis. Currently, this theory is replaced by the theory of "multiple hits" [16]. Genetic factors interact with metabolic and environmental factors, contributing to the accumulation of fat in hepatocytes, and consistently cause inflammation, cell death and fibrosis [3]. Recently, the cause and effect of insulin resistance in the development of NASH has been called into question, since NAFLD is often preceded and more predicted by the development of obesity, diabetes, dyslipidemia, arterial hypertension and cardiovascular disease [15].

Numerous pharmacological strategies have been tested in clinical trials for NAFLD therapy, and according to the aforementioned theory of NAFLD pathogenesis, different classes of drugs can be identified: antidiabetic drugs, antioxidants, prebiotics, drugs with anti-inflammatory, membranoprotective.

In order to prevent cardiovascular complications, it is imperative for these patients to treat cardiovascular risk factors, such as dyslipidemia, hypertension, and endothelial dysfunction [7].

Created a new original drug with endothelioprotective action by synthesis of the active substance (S) -2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolo-5-thioacetate (working name Angiolin), which combines fragments of thiotriazolin molecules and L-lysine of escinate and has high anti-ischemic, cardioprotective, neuroprotective, antioxidant and anti-inflammatory properties [5]. Intravenous administration of angiolin to animals with myocardial ischemia led to normalization of the ratio of thiol-disulfide system and nitric oxide system in the myocardium, and in rats with experimental chronic heart failure led to increased activity of endothelial NO-synthase, increased glutathione reductase activity of endothelial cells [18]. The use of the biologically active compound Angiolin in the complex treatment of NAFLD is rational in terms of its effect on metabolic processes occurring in the liver and for the purpose of correction of endothelial dysfunction, prevention of cardiovascular complications.

The *aim* - to characterize the structural and functional parameters of the liver in experimental steatohepatitis correction by biologically active compound Angiolin.

Materials and methods

Experimental studies were conducted on 110 white, non-linear, mature males weighing 180-200 g. Permission was obtained from the Bioethics Commission of National Pirogov Memorial Medical University, Vinnytsya (protocol №5 of March 27, 2014) to conduct the experiment. Animal retention and experiments were conducted in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 2005), and the "General Ethical Principles for Animal Experiments", adopted by the Fifth National Congress on Bioethics (Kyiv , 2013). Prior to the start of the experiments, the animals were quarantined for 10 days. During this period, the animals received a complete standard semi-synthetic starch-casein diet. Subsequently, the animals were divided into 2 groups: control - 30 intact animals that continued to be on the same diet under similar conditions with the animals of the experimental group, and experimental - 80 rats, which were created by the NASH model, for which for 8 weeks kept on a hypercaloric diet with high fat and high cholesterol containing about 30% fat (mainly saturated lipids) by adding cholesterol (obtained by mixing 2 g of cholesterol and 10 g of lard with 88 g of pellets of a normal balanced diet) [12, 28].

After the creation of the NASH model, the animals of the experimental group were further divided into five groups. Animals of the first experimental group (10 rats) were removed from the experiment and the necessary biochemical and morphological studies were performed.

Animals of the second experimental group (20 rats) were continued to be maintained on a high-fat diet (HFD), but an additional 50 mg/kg of Angiolin was administered intravenously over 4 weeks (HFD), but intraperitoneally.

Animals of the third experimental group (10 rats) also continued to be kept on HFD, but for an additional 30 days only Ringer-Locke solution (25 ml/kg) was intraperitoneally. Animals of the fourth experimental experimental group (20 rats) after the creation of the NASH model received a complete standard semisynthetic starch-casein diet and for 4 weeks was administered an additional 30 days Ringer-Locke solution (25 ml/kg) intraperitoneally. The animals of the fifth experimental group (20 rats) after the creation of the NASH model in addition to a full standard semisynthetic starch-casein diet for 4 weeks was administered a biologically active compound Angiolin at a dose of 50 mg per kg body weight (adjusted by Ringer-Locke solution) 25 mg/kg.

During the experiment, regular weekly weighing of the animals was performed to monitor the dynamics of the change in body weight of rats in grams (g). Body length (from nose to anus) was determined in centimeters (cm) to all rats. Body weight and body length were used to determine body mass index (BMI). BMI was calculated by the formula [2, 19]: BMI (g/cm2) = body weight / (body length) 2.

All animals under thiopental anesthesia (40 mg/kg) were sampled for biochemical study and liver tissue samples for morphological examination. The liver was weighed on an analytical balance. The relative weight of the liver was calculated by the formula: (liver weight / body weight)*100%.

After centrifugation, the following standard serum methods were used to determine the activity of enzyme markers of cytolysis - alanine aminotransferase (ALT), aspartate aminotransferase (AST) using the Wrightman and Frenkel colorimetric method, and cholestasis markers - alkaline phosphatase (ALPL) enzyme n-nitrophenilphosphate using

calorimetrimetry by Bodansky. Bilirubin content was determined by reaction with diazotized sulfanilic acid in the presence of a caffeine reagent (Endrashik method) according to the Bilirubin kit (Filitis-Diagnostics, Ukraine).

Macroscopic evaluation and description of the tissues of the liver of animals were performed after their extraction. To detect morphological abnormalities, tissue fragments of the left lobe of the liver were taken for histological examination, followed by their fixation in 10% neutral formalin neutral solution and paraffin filling according to the conventional method. The morphological condition of the liver in the experiment was evaluated on the basis of histological examination by staining drugs with hematoxylin, eosin, sudan III [4]. The micropreparations were examined using an SEO SSCAN light microscope and photo-documented using a Vision CCD Camera with histological specimens.

For electron microscopic examination, liver slices were fixed in 2.5% glutaraldehyde solution on 0.1 g phosphate buffer and fixed in 1% osmium tetroxide solution on phosphate buffer, 1% tannic acid solution, dehydrated in an alcohol battery, and a growing concentration of alcohol, in mixtures of acetone and epon and poured into a mixture of epon and araldite. The morphological structures were contrasted in the process of dehydration of the material with a saturated solution of uranyl acetate, and in sections with lead citrate. Sections 40-60 nm thick, obtained on a UMTP-7 ultramicrotome, and were examined in a PEM-125 K. electron microscope.

Statistical analysis of the obtained results was performed using the licensed program "STATISTICA 8" by Statsoft, using parametric and non-parametric methods of estimation of the obtained results. Data are presented in the form of median (Me) and interquartile range (Q1-Q3). The normality of distribution was checked using the Kolmogorov-Smirnov test. The non-parametric Mann-Whitney U rank test was used for the asymmetric distribution. The statistical significance of the difference between the comparative values was considered significant at $p<0.05$.

Results

Anthropometric indices of experimental rats significantly changed during the experiment. The use of HFD for 60 days resulted in an increase in body weight of 1.66 times, and after 90 days - of 1.87 times, with the body mass index (BMI) increasing by 1.32 and 1.39 times, respectively. Liver weight reached 10.91 g after model creation, and after 12 months it reached 12.68 g. Relative liver weight was increased by 12.15% and 15.06%, respectively, compared to the control. The use of Angiolin - (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate, after the creation of a model of NASH without abrogation of HFD resulted in a decrease in the body weight of rats by 15.12%, BMI - by 6.52%, liver weight by 21.61%, relative liver weight by 7.65%. The use of a standard semi-synthetic starch-casein diet after the creation of the NASH model led to a decrease in the body weight of rats by only 14.55%, BMI - 6.33%, liver weight - 19.01%, relative liver weight - 5.21%.

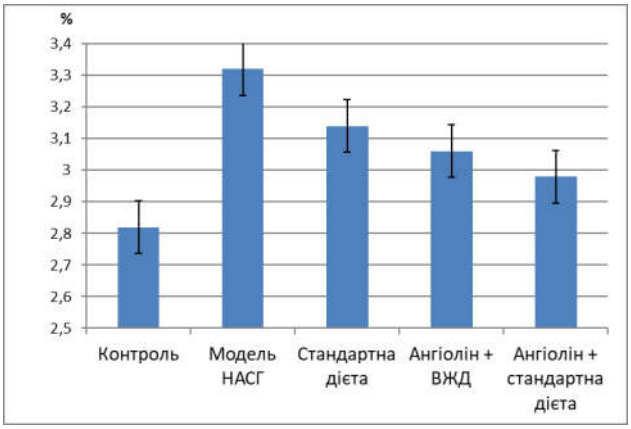

Fig. 1. Changes in the relative weight of the liver after the creation of a model of non-alcoholic steatohepatitis in rats and its correction.

The use of the biologically active compound Angiolin at a dose of 50 mg per kg body weight after the creation of the NASH model in addition to a full standard semi-synthetic starch-casein diet for 4 weeks showed statistically significant results. The body weight of experimental animals was lower by 18.67%, BMI - by 10.02%, liver weight - by 26.97%, relative liver weight - by 10.24% compared with rats without treatment (Fig. 1). Macroscopically, the liver was enlarged, yellow with a bold gloss on the incision.

The obtained experimental results showed that the test compound Angiolin has a hepatoprotective effect. A study of the intensity of cytolysis syndrome in rats with the correction of the NASH experimental model showed that there was less ALT activity using Angiolin along (by 20.52%, $p<0.05$) and Angiolin with the standard semi-synthetic starch-casein diet (by 33.61% $p<0.05$) compared with the activity of untreated animals with the NASH model. Gamma-glutamyltranspeptidase activity was also lower using the compound compared to non-treated animals: by 20.19% with Angiolin ($p<0.05$) and by 32.86% with Angiolin along with standard semi-synthetic starch-casein diet. The activity of AST did not come close to the control values using the compound, however, this figure was statistically different by 28.61% ($p<0.05$) after treatment with angiolin together with the standard semi-synthetic starch-casein diet compared to untreated animals. Increasing biochemical markers of liver tissue damage on the background of insulin resistance indicates the presence of structural and functional changes in hepatocytes with the development of cytolysis and cholestasis syndromes.

Since the biochemical markers of cholestasis syndrome are the level of total, direct bilirubin and ALPL activity, we evaluated the level of these indicators to assess the effectiveness of angiolin. The indicator that most clearly presented cholestasis syndrome in rats with the NAFLD model was ALPL activity, which in untreated animals was 30.82% higher ($p<0.05$) compared to the intact group. Less activity of ALPL compared with the untreated group was with the administration of Angiolin (18.04%, $p<0.05$) and with the

administration of Angiolin along with the standard semi-synthetic starch-casein diet (29.79%, p<0.05). In the study of total and direct bilirubin content, it was noted that after NASH modeling, the total bilirubin level increased by 20.46% and direct bilirubin by 8.19%. Increased total, direct bilirubin and LF activity confirms the development of cholestasis syndrome with impaired biliary function of the liver with impaired bile duct formation and damage to small bile ducts. Using Angiolin, the levels of these indicators were statistically significantly lower: by 10.74% and by 5.43%, respectively.

A histomorphological study of the liver of intact rats revealed a typical structure of the liver lobules. The boundaries of the liver lobules were determined only by the location of the interspecies vessels and bile ducts constituting the "triads". Each triad has an interparticle artery, an interparticle vein and a bile duct. Round-shaped hepatocytes with eosinophilic cytoplasm and basophilic nucleus were found. Diploid hepatocytes were detected in places in the liver. The liver lobes consisted of well-defined beams radially diverging from the central vein. Sinusoids, moderately filled with red blood cells, lay between the beams. The portal tracts were medium in size. The diameter of the veins was much larger than the arteries. A small number of stellate cells were detected. Between the lobes was the connective tissue. The cytoplasm had no pronounced vacuolation.

Conducted morphological study of the liver of rats after 60 days of feeding of HFD revealed a significant accumulation of lipids in hepatocytes, which caused cell hypertrophy, narrowing of the sinus lumines.

There was a plethora of central veins. Fatty hepatocyte dystrophy had the appearance of microvesicular and macrovascular vacuolation. A significant increase in hepatocyte size was found compared to the control group of animals. The filling of the cytoplasm with fatty drops caused deformation of the nuclei and displacement of them to the periphery of the cell (Fig. 2).

Many of the hepatocytes had signs of dystrophy. The cells became hypertrophic, changing their shape to more rounded in parallel with decreased basophilia and vacuolation of the cytoplasm with lipid inclusions. The greatest accumulation of lipids was observed in hepatocytes near the portal areas, with lipid vacuoles occurring both large and small in size. At predominantly macrovesicular vacuolation, the cytoplasm had an optically empty appearance, the nucleus shifted to the periphery of the cell (Fig. 3). The nature of the histological pattern of the liver tissue at 60 days of Feeding the Iron can be identified as steatohepatitis. Electron microscopic studies have shown that in experimental NASH (after 60 days of retention on HFD) significant changes in the plasma, nuclear and intracellular membranes of endothelial cells and hepatocytes develop in the liver against the background of microcirculation disturbance. Destabilization and destruction of cell membranes and organelle membranes adversely affect the metabolic and functional capacity of the organ [22].

The obtained results of a morphological study of the liver

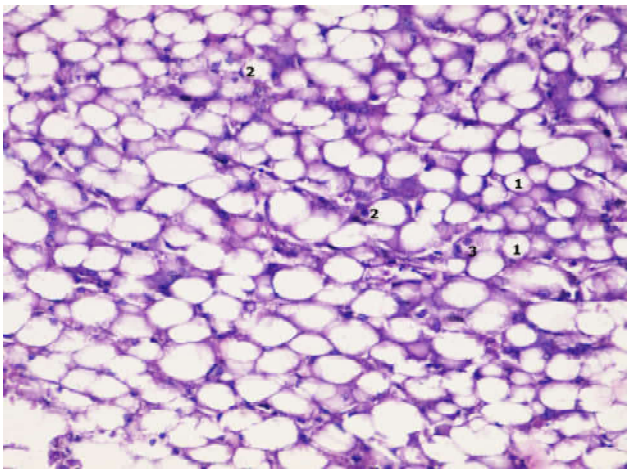

Fig. 2. The liver of the rat for 60 days of feeding the HFD. Diffuse mainly macrovesicular fatty degeneration of hepatocytes. Hematoxylin-eosin, x200. (1 - lipid droplets in the cytoplasm of hepatocytes, 2 - displacement of the hepatocyte nucleus to the periphery of the cell with a lipid droplet, 3 - dual-core hepatocytes).

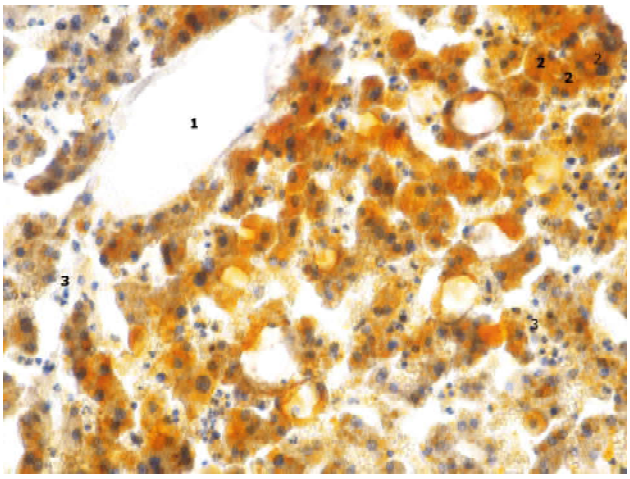

Fig. 3. The liver of the rat for 90 days of feeding the HFD. Preferably macrovesicular fatty degeneration of hepatocytes. Sudan III, x400. (1 - central vein, 2 - fat droplets of different sizes, 3 - sinusoidal hemocapillaries).

tissue of experimental animals with the NASH model on the background of the administration of the biologically active compound Angiolin at a dose of 50 mg / kg for a month indicated a partial restoration of the lobular structure of the liver parenchyma compared with animals with the NASH model without correction. The morphological structure of the liver was characterized by a decrease in fatty infiltration of hepatocytes, a partial restoration of the architectonics of hepatic beams, an increase in the number of binucleate hepatocytes (Fig. 4). However, hypertrophied hepatocytes and hepatocytes with focal fat inclusions in the cytoplasm were still detected.

We have studied the endothelial protective effect of the compound Angiolin. Our studies [23] of the submicroscopic state of animal liver endothelial cells in the correction of NASH by angiolin have established that the ultrastructural

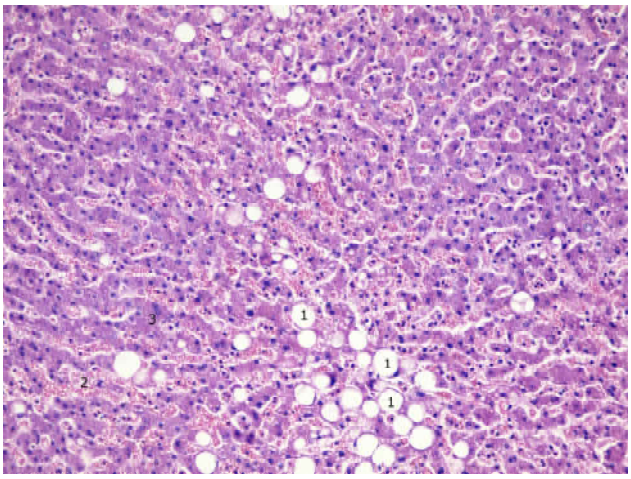

Fig. 4. Liver of the rat for 90 days of the experiment (60 days of feeding of HFD + application of Angiolin). Focal predominantly macrovascular fatty degeneration of hepatocytes. Hematoxylin-eosin, x200. (1 - lipid droplets in the cytoplasm of hepatocytes, 2 - sinusoids, 3 - hypertrophied hepatocytes).

organization of endothelial cells has a typical long elongated shape. Elliptical nuclei include a karyoplasm made of euchromatin, which is confined to a karyolemma with clear nuclear membranes. Between them, there is a relatively uniform perinuclear space, and many nuclear pores are noted. The nuclear site of endothelial cell cytoplasm involves many small, small-sized organelles. The tubules of the granular endoplasmic reticulum and the enlightened matrix of individual mitochondria are somewhat enlarged. Narrow cytoplasmic sections of endothelial cells have well-defined perforations. Numerous microvilli are observed in Disse spaces and are well contoured.

Discussion

According to the literature [6], lipids contained in lipid droplets in the liver are dynamic and refer to metabolically active substances. Lipid droplets consist of the nucleus of triacylglycerols with or without cholesterol esters and the peripheral monolayer of phospholipids [24]. Inactive PNPLA3 has been shown to accumulate on the surface of lipid droplets and is associated with an increase in macrovesicular steatosis [25]. The inflammatory response does not always coincide with the prevalence of lipid droplets, indicating different mechanisms of lipid deposition and hepatocyte infiltration [26]. In addition, it is of interest to present a new theory that the trigger mechanism of hepatocyte dysfunction is lipotoxicity, which leads to disease progression in NASH. According to this theory, lipotoxic damage occurs under conditions of excessive movement of free fatty acids, especially saturated fatty acids, rather than through simple steatosis. It is likely that lipid accumulation occurs in parallel with the formation of lipotoxic metabolites, which are primarily responsible for the progression of liver disease and the development of insulin resistance [20].

According to the literature, liver cell damage and apoptosis are stimuli for the activation of mitogenic potential - liver cells on the background of steatosis / steatohepatitis are actively dividing and tend to accumulate less and less fat [1]. In the course of further evolution, apoptotic altered hepatocytes are transformed into small eosinophilic bodies of Counsilman [29]. Comparing the degree of reverse ultrastructural changes of endothelial cells and hepatocytes under the conditions of correction of the steatosis of the biologically active compound Angiolin at a dose of 50 mg per kg of body weight and when applied for 4 weeks hepatoprotector ademetionin at a dose of 21 mg per kg of body weight, damage to the structural components of the liver lobules. However, there are some differences. Thus, Angiolin correction showed better regeneration of sinusoidal hemocapillaries and hepatocytes and a better state of microvilli from the plasmolemma of the vascular section of hepatocytes.

In the future, it is promising to investigate the effect of Angiolin on the function of endothelial cells of the sinusoids of the liver and the secretion of biologically active substances produced by the endothelium.

Conclusion

The use of biologically active compound Angiolin once a day for 30 days allows to reduce cytolysis syndrome (to reduce biochemical parameters such as alanine aminotransferase activity, aspartate aminotransferase, gamma-glutamyltranspeptidase), reduce cholestasis syndrome (decrease in alkaline phosphatase level) hepatocytes, which will indicate the normalization of structural and functional state.

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ОСОБЛИВОСТІ СТРУКТУРНИХ ТА ФУНКЦІОНАЛЬНИХ ПАРАМЕТРІВ ПЕЧІНКИ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО СТЕАТОГЕПАТИТУ ТА ЙОГО КОРЕКЦІЇ У ЩУРІВ З ОЖИРІННЯМ

Півторак К.В.

Удосконалення фармакологічної стратегії неалкогольної жирової хвороби печінки основано на вивченні впливу фармпрепаратів на структуру та функцію печінки. Патогенез неалкогольного стеатогепатиту є складним і багатофакторним, в основному за участю генетичних, метаболічних факторів і факторів навколишнього середовища. Мета дослідження - охарактеризувати структурні та функціональні параметри печінки при корекції експериментального стеатогепатиту біологічно активною сполукою Ангіолін. Експериментальне дослідження виконано на 110 статевозрілих білих щурах-самцях масою 180-220 грамів, котрих утримували на стандартному раціоні віварію. Усіх тварин розподілили

на 2 групи: контрольну (30 інтактних тварин) та дослідну (80 тварин). Усім тваринам дослідної групи створювали модель неалкогольного стеатогепатиту, для чого протягом 8 тижнів утримували на гіперкалорійній дієті з високим вмістом жирів та холестерину. Частину тварин (10 щурів) виводили з досліду шляхом внутрішньо-плеврального введення тіопенталу-натрію (50 мг/кг) та проводили необхідні біохімічні та морфологічні дослідження, частину тварин (30 щурів) ще протягом 4 тижнів продовжували утримувати на високожировій дієті та вводили біологічно активну сполуку Ангіолін (20 щурів), а 10 щурам лише розчин Рінгера-Локка. Інших тварин дослідної групи (40 щурів) після створення моделі перевели на повноцінну стандартну напівсинтетичну крохмально-казеїнову дієту та протягом 4 тижнів вводили (20 щурів) біологічно активну сполуку Ангіолін, а 20 щурам лише розчин Рінгера-Локка. Макроскопічну оцінку та описання печінки тварин проводили після вилучення тварин із експерименту під тіопенталовим наркозом. Статистичний аналіз отриманих результатів проведений у програмі "STATISTICA 8" з використанням параметричних і непараметричних методів оцінки отриманих результатів. Встановлено, що застосування Ангіоліну 1 раз на добу протягом 30 днів дозволяє зменшити синдром цитолізу (знижується активність аланінамінотрансферази, аспартатамінотрансферази, гамма-глутаміltранспептидази), зменшити синдром холестазу (рівень лужної фосфатази зменшується), покращити морфологічний стан гепатоцитів та нормалізувати функцію печінки.

Ключові слова: *хвороби печінки, стеатогепатит, моделювання, морфологія, корекція.*

ОСОБЕННОСТИ СТРУКТУРНЫХ И ФУНКЦИОНАЛЬНЫХ ПАРАМЕТРОВ ПЕЧЕНИ В УСЛОВИЯХ ЭКСПЕРИМЕНТАЛЬНОГО СТЕАТОГЕПАТИТА И ЕГО КОРРЕКЦИИ У КРЫС С ОЖИРЕНИЕМ

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Усовершенствование фармакологической стратегии неалкогольной жировой болезни печени основано на изучении влияния фармпрепаратов на структуру и функцию печени. Патогенез стеатогепатита является сложным и многофакторным, в основном с участием генетических, метаболических факторов и факторов окружающей среды. Цель исследования - охарактеризовать структурные и функциональные параметры печени при коррекции экспериментального стеатогепатита биологически активным соединением Ангиолина. Экспериментальное исследование выполнено на 110 половозрелых белых крысах-самцах массой 180-220 граммов, которых содержали на стандартном рационе вивария. Всех животных разделили на две группы: контрольную (30 интактных животных) и опытную (80 животных). Всем животным опытной группы создавали модель неалкогольного стеатогепатита, для чего в течение 8 недель удерживали на гиперкалорийной диете с высоким содержанием жиров и холестерина. Часть животных (10 крыс) выводили из опыта путем внутриплеврального введения тиопентала натрия (50 мг/кг) и проводили необходимые биохимические и морфологические исследования, часть животных (30 крыс) еще в течение 4 недель продолжали удерживать на высокожировой диете и 20 крысам вводили биологически активное соединение Ангиолина, а 10 крысам только раствор Рингера-Локка. Других животных опытной группы (40 крыс) после создания модели перевели в полноценную стандартную полусинтетическую крахмало-казеиновую диету и в течение 4 недель вводили (20 крыс) биологически активное соединение Ангиолина, а 20 крысам только раствор Рингера-Локка. Макроскопическая оценка и описание печени животных проводилось после выведения животного из эксперимента под тиопенталовым наркозом. Статистический анализ полученных результатов проведен в программе "STATISTICA 8" с использованием параметрических и непараметрических методов оценки полученных результатов. Установлено, что применение Ангиолина 1 раз в сутки в течение 30 дней позволяет уменьшить синдром цитолиза (снижается активность АЛТ, АСТ, гамма-глутамилтранспептидазы), уменьшить синдром холестаза (уровень щелочной фосфатазы снижается), улучшить морфологическое состояние гепатоцитов и нормализовать функцию печени.

Ключевые слова: *болезни печени, стеатогепатит, моделирование, морфология, коррекция.*

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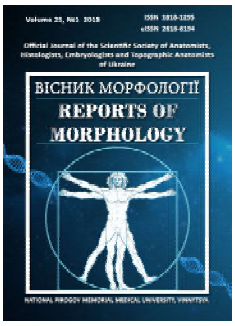

Signs of palmar dermatoglyphics as markers of atopic diseases

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The family character of atopic conditions, confirmed by many studies, has become the basis for the use of the method of dermatoglyphics to clarify the genetic nature of the "atopic march". The purpose of the study was to identify differences in the features of palmar dermatoglyphics between patients with atopic dermatitis, allergic rhinitis and bronchial asthma. Primary indexes of palmar dermatoglyphics of young men and young women patients with atopic dermatitis, allergic rhinitis and bronchial asthma were taken from the data bank of the research center of National Pirogov Memorial Medical University, Vinnytsya. According to the method of Cummins H. and Midlo Ch. dermatoglyphic study of 320 young men and young women with allergic rhinitis (n = 69), bronchial asthma (n = 108) and atopic dermatitis (n = 143) was performed. Quantitative indices of palmar dermatoglyphics were subject to analysis. The results obtained were processed using the Statistica 6.1 license package using non-parametric methods. It is established that the differences of quantitative indices of palmar dermatoglyphics between young men / young women with atopic dermatitis and allergic rhinitis cover 50.0% / 66.67%; among patients with atopic dermatitis and bronchial asthma - 38.89% / 33.33%; among patients with allergic rhinitis and bronchial asthma - 22.22% / 55.56% respectively. Thus, in young men, the marker potential for signs of palmar dermatoglyphics in the prognosis for the development of bronchial asthma in the presence of allergic rhinitis (22.22%) or atopic dermatitis (38.89%) are insignificant compared with the prognosis for the development of allergic rhinitis in the presence of atopic dermatitis (50.0%). In young women, the marker features of palmar dermatoglyphics in the prognosis for the development of bronchial asthma in the presence of atopic dermatitis are insignificant (33.33%) compared with the prognosis for the development of bronchial asthma in the presence of allergic rhinitis (55.56%) and the prognosis for the development of allergic rhinitis (66.67%).

Keywords: *palmar dermatoglyphics, atopic dermatitis, bronchial asthma, allergic rhinitis.*

Introduction

Dermatoglyphics (from ancient Greek δέρμα "skin" and γλύφω "carving") is a section of morphology that studies specific patterns on the skin of hands and feet formed by ridges. Dermatoglyphic features have long been used in various fields: in medicine - as a marker of many chromosomal and multifactorial diseases [1, 19]. Also features of human skin image are used in such fields as criminalistics and forensic medicine [16].

A striking example of multifactorial diseases are atopic dermatitis (AD), bronchial asthma (BA), and allergic rhinitis (AR), which are chronic inflammatory processes that underlie both exogenous and endogenous factors [3, 20]. There is still no consensus among scientists about the key trigger mechanism in the pathogenesis of these diseases [17, 30, 31].

The prevalence of these diseases covers the whole world. Up to 65.0 % of people with AD have their first symptoms from the age of 18 months. By the age of 7, only half of patients have complete disease completion and only 60.0 % have completed disease by adulthood. In addition, about in 30.0 % of AD patients develop asthma [26]. A 2001-2005 study of British scientists found that frequency of asthma had decreased in all patients ((2001: 6.9 (95.0 % CI 6.8-7.0); 2005: 5.2 (95.0 % CI 5.1-5.3) per 1000 patient years, p<0.001)). However, the prevalence rate of BA in adulthood increased (15-44 years: 23.3 %; 45-64 years: 27.7 %; over 65 years: 21.5 %) [24].

However, it is unambiguously proved that the human

constitution influences both the risk of occurrence and the manifestation and severity of these diseases [10, 18, 22, 23, 27, 28]. Jo Y.M. and Yi J.S. [12], in a study of a sample of schoolchildren, found a relationship between the onset of AR and gender, high school class, living space, stress level, vegetable consumption, and sleep satisfaction.

266 AD patients and 532 healthy individuals were examined in Harbin, China. The study found that obesity was significantly correlated with the presence of the disease (OR = 3.2, 95.0 % CI: 1.8, 5.7). Men and women had similar associations (OR = 3.1 for men and 3.2 for women) [15].

Holguin F. et al. [11] investigated the effect of weight on asthma. The study population was 1,049 individuals, 48.0 % of whom had late asthma ($\geq$12 years) and 52.0 % had asthma at an early age (<12 years). Compared with patients with obesity with asthma after 12 years, patients with obesity and with asthma up to 12 years had worse rates.

In particular, studies have been conducted by foreign authors from different parts of the world to study the features of skin pattern in individuals suffering from these diseases.

A group of researchers from India [25] conducted a study to identify specific dermatoglyphic markers of susceptibility to asthma. It was found that such persons are characterized by: decrease in the number of arches, increase in the number of ulnar loops in comparison with the control group was revealed as a result of the study.

In addition, similar studies have been performed for other diseases such as psoriasis, vitiligo, and focal alopecia [14, 21]. The features of dermatoglyphic pattern in AD, BA and AR among the population of Ukraine is still a poorly understood topic [4], and therefore requires more detailed data collection and analysis.

The *purpose* of the study is to identify differences in the features of palmar dermatoglyphics between patients with AD, AR and BA.

Materials and methods

From National Pirogov Memorial Medical University, Vinnytsya Research Center obtained primary indexes of palmar dermatoglyphics in patients with AR, BA and AD of young men and young women. In previous studies, these results have been used when compared with healthy young men and young women [2, 6, 8]. The diagnosis of AD was consistent with conventional methods [9], the diagnosis of BA - according to the recommendations of the International Expert Group EPR-2, and the AR - according to the recommendations of ISSA. Dermatoglyphs of 36 young men and 33 young women with AR were studied; 63 young men and 45 young women with BA; 64 young men and 79 young women with AD.

The analysis of quantitative indices of palmar dermatoglyphics was performed according to the method of Cummins H. and Midlo Ch. [5]. Determined the size of the angles ∠atd, ∠ctd, ∠atb, ∠btc, ∠dat; the length of the segment c-t; ridge count ab, bc; Cummins index was determined based on the stroke of the major palmar lines A and D.

The results obtained were processed using the Statistica 6.1 license package using non-parametric methods.

Results

Significant differences or trends of differences in the quantitative indices of palmar dermatoglyphics between patients with AR, BA and AD (Table 1) were established.

When comparing the quantitative indices of the palmar dermatoglyphics of *young men with AR with patients with BA*, significant differences were found in the size of the inner angles ∠btc and ∠ctd of the left palm, as well as - in the course of the main palmar lines, which was reflected in larger values of Cummins index of both palms in patients with AR. Thus, of the 18 indices of both palms analyzed, 4 of them showed significant differences between young men with AR and BA (see Table 1).

In *young men with AR compared with AD patients*, the ridge count a-b of both palms, the dimensions of the inner angles ∠atb of the left palm, ∠ctd and the total angle ∠atd of both palms are significantly smaller and the inner angle ∠btc is larger. Thus, out of 18 indices of both palms analyzed, 9 of them showed significant differences between young men with AR and AD (see Table 1).

When comparing the quantitative indices of the palmar dermatoglyphics of *young men with AD compared with patients with BA*, the dimensions of the internal angles ∠atb, ∠ctd and the total angle ∠atd and Cummins index of both palms are significantly smaller. Thus, out of 18 indices of both palms analyzed, 7 of them showed significant differences between young men with AD and BA(see Table 1).

When comparing the quantitative indexes of the palmar dermatoglyphics of *young women with AR with patients with BA*, it is found that the dimensions of the inner angles ∠btc of the right palm, ∠atb and the total angle ∠atd of both palms are significantly smaller. In this case, the length of the line connecting the triradi ∇c and the axial ∇t of the left palm and the Cummins index of the right palm are significantly larger, and the ridge count a-b of both palms and b-c of the right palm are significantly smaller. Thus, of the 18 indices of both palms analyzed, 10 of them showed significant differences between young women with AR and BA (see Table 1).

In *young women with AR compared with patients with AD*, the ridge count a-b of both palms, the dimensions of the inner angles ∠atb, ∠ctd and the total angle ∠atd of both palms are significantly smaller, and the angle ∠dat and the length of the segment c-t of both palms are larger. Thus, of the 18 indices of both palms analyzed, 12 of them showed significant differences between young women with AR and AD (see Table 1).

When comparing the quantitative indexes of the palmar dermatoglyphics of *young women with AD compared with*

Table 1. Quantitative indices of palmar dermatoglyphics in Podillia people of different gender with AR, BA and AD (M±σ).

Indicator	Gender	Patients with AR (n_M=36, n_F=33) (1)	Patients with BA (n_M=63, n_F=45) (2)	Patients with AD (n_M=64, n_F=79) (3)	p_{1-2}	p_{1-3}	p_{2-3}
R - ATD (degrees)	M	40.97±4.90	41.57±5.88	43.91±7.27	>0.05	<0.05	<0.05
	F	40.60±4.75	44.13±5.35	44.56±5.86	<0.01	<0.001	>0.05
L - ATD (degrees)	M	40.85±4.14	40.47±5.52	43.44±7.12	>0.05	<0.05	<0.01
	F	40.61±4.25	44.08±5.17	45.38±6.18	<0.01	<0.001	>0.05
R - CTD (degrees)	M	13.76±4.19	14.34±4.66	16.95±3.82	>0.05	<0.001	<0.001
	F	14.97±2.92	15.97±3.94	16.96±3.20	>0.05	<0.01	>0.05
L - CTD (degrees)	M	13.68±3.94	16.01±5.37	16.23±3.61	<0.05	<0.01	>0.05
	F	16.00±2.82	17.17±3.36	17.43±3.43	>0.05	<0.05	>0.05
R - ATB (degrees)	M	15.79±2.99	15.88±2.80	16.86±2.68	>0.05	=0.069	<0.05
	F	14.94±3.53	16.86±3.31	17.04±2.82	<0.05	<0.01	>0.05
L - ATB (degrees)	M	15.64±2.66	15.81±2.81	17.50±3.05	>0.05	<0.01	<0.01
	F	14.39±3.17	17.20±3.45	18.11±3.08	<0.001	<0.001	>0.05
R - BTC (degrees)	M	11.73±2.88	10.63±2.98	10.50±2.46	=0.077	<0.05	>0.05
	F	10.69±2.62	13.06±2.68	10.82±2.21	<0.001	>0.05	<0.001
L - BTC (degrees)	M	11.74±3.23	9.95±2.33	10.20±2.71	<0.01	<0.05	>0.05
	F	10.34±3.08	11.13±2.70	10.34±2.48	>0.05	>0.05	>0.05
R - DAT (degrees)	M	58.68±5.24	57.22±6.25	57.30±5.93	>0.05	>0.05	>0.05
	F	59.77±4.99	61.00±6.58	56.19±5.66	>0.05	<0.01	<0.001
L - DAT (degrees)	M	58.18±4.32	58.98±5.33	58.20±5.72	>0.05	>0.05	>0.05
	F	58.22±3.99	60.24±7.58	55.94±5.21	>0.05	<0.05	<0.001
R - CT (mm)	M	74.97±9.76	76.54±8.37	76.07±10.95	>0.05	>0.05	>0.05
	F	73.83±8.09	71.20±8.19	69.27±9.57	>0.05	<0.05	>0.05
R - CT (mm)	M	74.71±8.48	77.85±7.45	76.39±10.45	=0.058	>0.05	>0.05
	F	74.29±6.11	70.31±9.62	68.50±9.87	<0.05	<0.01	>0.05
R - AB (absolute units)	M	36.55±6.60	38.82±6.05	40.09±6.20	=0.086	<0.01	>0.05
	F	33.56±8.69	40.53±7.40	40.95±5.89	<0.001	<0.001	>0.05
L - AB (absolute units)	M	37.94±8.07	39.74±7.41	41.30±5.85	>0.05	<0.05	>0.05
	F	33.94±10.58	41.31±9.29	41.41±5.41	<0.01	<0.001	>0.05
R - BC (absolute units)	M	28.27±5.45	26.87±4.62	27.50±6.21	>0.05	>0.05	>0.05
	F	27.06±6.47	32.02±6.19	27.60±5.62	<0.001	>0.05	<0.001
L - BC (absolute units)	M	28.90±5.36	26.77±5.21	27.11±5.81	=0.056	>0.05	>0.05
	F	26.77±6.26	28.77±5.56	26.90±5.52	>0.05	>0.05	=0.073
R - I (absolute units)	M	8.600±1.886	5.910±1,780	9.281±1.713	<0.001	=0.069	<0.001
	F	8.743±1.597	5.200±1.590	8.899±1.959	<0.001	>0.05	<0.001
L - I (absolute units)	M	7.065±1.948	4.050±1.940	7.641±1.811	<0.001	>0.05	<0.001
	F	8.083±2.089	8.480±2.070	7.595±1.978	>0.05	>0.05	<0.05

Notes: ATD - atd angle value; CTD - ctd angle value; ATB - atb angle value; BTC - btc angle value; DAT - dat angle value; CT - the distance between the palmar triradi c and t; AB - palmar ridge count a-b; BC - palmar ridge count b-c; I -Cummins index; R - right palm; L - left palm.

patients with BA, it is found that the ridge count b-c and the dimensions of the inner angle ∠btc of the right palm, as well as the angle ∠dat of both palms are significantly smaller, and Cummins index of both is significantly larger. Thus, out of 18 indices of both palms analyzed, 6 of them showed significant differences between young women with AD and BA (see Table 1).

Discussion

AD, AR, and BA in 80.0 % of cases are a family syndrome associated with genetic defects [13]. It is known that the risk of developing AD is 60.0-80.0 % in a child if both parents have atopic diseases [29]. Polygenic control of the pathogenetic mechanisms of atopy is envisaged [7], which includes the combined influence of both genes responsible for the body's immune response to antigen and genes responsible for the structure of organs that perform barrier function with the environment.

A number of authors have revealed diagnostic and prognostic signs of the development of AD by comparing palmar dermatoglyphics in patients with AD in the stage of remission with healthy peers, to which the young men attributed combinations of the following signs: angles ∠atd, ∠ctd, ∠atb, segment a-d; ridge count a-b, b-c and c-d on both palms with high values; Cummins index of the left palm with low values; in young women - angles ∠atd, ∠ctd, ∠atb on both palms and ∠bts on the right palm with high values; segment a-d, ridge count a-b, b-c on both palms and c-d on the right palm with high values and segment c-t on both palms with smaller values [6].

Year-round rhinitis in young women is known to be associated with a narrower angle ∠atb and in sick young men with a wider angle ∠atb in both palms compared to the mean population values, and in both of them with a wider angle ∠dat at right palm accompanied by low Cummins index values [2].

According to Gunas I.V. and others [8], palmar dermatoglyphics of patients' young men with asthma compared to healthy peers are represented by Cummins index with low values, palm angles ∠dat and ∠atd and ridge count a-b and b-c with higher values.

The results obtained by dermatoglyphics indirectly confirm the presence of a tendency to develop diseases of atopic nature. Thus, it is shown that the largest number of significant differences in quantitative indices of palmar dermatoglyphics were recorded between *patients with AR and patients with AD* both young men (50.0 %) and young women (66.67 %). Moreover, these differences are almost unidirectional in nature regardless of sex and are found in the radial and ulnar areas of the palm, which is related to the peculiarities of localization of the palm triradii ∇a, ∇b,∇c, ∇d. It should be emphasized that the differences in the dimensions of the angles refer to both the internal and the overall angle ∠atd.

Almost the same number of significant differences in the quantitative indices of palmar dermatoglyphics were recorded between *AD patients* and *BA patients* both young men (38.89 %) and young women (33.33 %), but they were different in nature. Thus, the differences between young men are recorded in the ulnar and radial regions of the palm, and in young women - in the medial region of the palm; young men have differences about the size of both internal and overall angles of ∠atd, while in young women - only internal angles.

Finally, the differences between the *patients with AR* and the *patients with BA* young men (22.22 %) and young women (55.56 %) are quite different in both quantitative and localization of changes. The differences in young men are found in the ulnar and medial regions of the left palm, and do not include the size of the total angle ∠atd, and in young women - radial region of both palms and the medial region of the right palm, and include the total angle ∠atd of both palms.

In general, the differences in the quantitative indices of palmar dermatoglyphics between patients with AD, AR and BA were found to be more pronounced in young women than in young men, which is in the logical context of the statement regarding the more frequent connection with atopic diseases on the maternal line (60.0-70.0 %) than according to the father [29].

Conclusions

1. In young men, the marker potential for signs of palmar dermatoglyphics in the prognosis of the development of BA in the presence of AR (22.22 %) or AD (38.89 %) are insignificant compared with the prognosis of the development of AR in the presence of AD (50.0 %).

2. In young women, the marker potential of the features of palmar dermatoglyphics regarding the prognosis of BA in the presence of AD are insignificant (33.33 %) compared with the prognosis of BA in the presence of AR (55.56 %) and the prognosis of the development of AR in the presence of AD (66.67 %).

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ОЗНАКИ ДОЛОННОЇ ДЕРМАТОГЛІФІКИ ЯК МАРКЕРИ ЗАХВОРЮВАНЬ АТОПІЧНОЇ ПРИРОДИ

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Сімейний характер атопічних станів, підтверджений даними багатьох досліджень, став підставою для застосування методу дерматогліфіки задля уточнення генетичної природи "атопічного маршу". Мета дослідження - виявити розбіжності ознак долонної дерматогліфіки між хворими на атопічний дерматит, алергічний риніт та бронхіальну астму. Первинні показники долонної дерматогліфіки юнаків і дівчат, хворих на атопічний дерматит, алергічний риніт та бронхіальну астму взяті з банку даних науково-дослідного центру Вінницького національного медичного університету ім. М.І. Пирогова. За методикою Cummins H. і Midlo Ch. проведено дерматогліфічне дослідження 320 юнаків і дівчат, хворих на алергічний риніт (n=69), бронхіальну астму (n=108) та атопічний дерматит (n=143). Аналізу підлягали кількісні показники долонної

дерматогліфіки. Отримані результати оброблені за допомогою ліцензійного пакета "Statistica 6.1" з використанням непараметричних методів. Встановлено, що розбіжності кількісних показників долонної дерматогліфіки між юнаками / дівчатами, хворими на атопічний дерматит й алергічний риніт охоплюють 50,0% / 66,67%; між хворими на атопічний дерматит та бронхіальну астму - 38,89% / 33,33%; між хворими на алергічний риніт та бронхіальну астму - 22,22% / 55,56% відповідно. Таким чином, у юнаків маркерні можливості ознак долонної дерматогліфіки щодо прогнозу розвитку бронхіальної астми при наявності у них алергічного риніту (22,22%) або атопічного дерматиту (38,89%) є незначними порівняно з прогнозом розвитку алергічного риніту при наявності атопічного дерматиту (50,0%). У дівчат маркерні можливості ознак долонної дерматогліфіки щодо прогнозу розвитку бронхіальної астми при наявності атопічного дерматиту є незначними (33,33%) порівняно з прогнозом розвитку бронхіальної астми при наявності алергічного риніту (55,56%) та прогнозом розвитку алергічного риніту при наявності атопічного дерматиту (66,67%).
Ключові слова: *долонна дерматогліфіка, атопічний дерматит, бронхіальна астма, алергічний риніт.*

ПРИЗНАКИ ЛАДОННОЙ ДЕРМАТОГЛИФИКИ КАК МАРКЕРЫ ЗАБОЛЕВАНИЙ АТОПИЧЕСКОЙ ПРИРОДЫ

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Семейный характер атопических состояний, подтвержденный данными многих исследований, стал основанием для применения метода дерматоглифики для уточнения генетической природы "атопического марша". Цель исследования - выявить расхождения признаков ладонной дерматоглифики между больными атопическим дерматитом, аллергическим ринитом и бронхиальной астмой. Первичные показатели ладонной дерматоглифики юношей, больных атопическим дерматитом, аллергическим ринитом и бронхиальной астмой взяты из банка данных научно-исследовательского центра Винницкого национального медицинского университета имени Н.И.Пирогова. По методике Cummins H. и Midlo Ch. проведены дерматоглифические исследования 320 юношей, больных аллергическим ринитом (n = 69), бронхиальной астмой (n = 108) и атопическим дерматитом (n = 143). Анализу подлежали количественные показатели ладонной дерматоглифики. Полученные результаты обработаны с помощью лицензионного пакета "Statistica 6.1" с использованием непараметрических методов. Установлено, что различия количественных показателей ладонной дерматоглифики между юношами / девушками, больными атопическим дерматитом и аллергическим ринитом охватывают 50,0% / 66,67%; между больными атопическим дерматитом и бронхиальной астмой - 38,89% / 33,33%; между больными аллергическим ринитом и бронхиальной астмой - 22,22% / 55,56% соответственно. Таким образом, у юношей маркерные возможности признаков ладонной дерматоглифики по прогнозу развития бронхиальной астмы при наличии у них аллергического ринита (22,22%) или атопического дерматита (38,89%) незначительны по сравнению с прогнозом развития аллергического ринита при наличии атопического дерматита (50,0%). У девушек маркерные возможности признаков ладонной дерматоглифики по прогнозу развития бронхиальной астмы при наличии атопического дерматита незначительны (33,33%) по сравнению с прогнозом развития бронхиальной астмы при наличии аллергического ринита (55,56%) и прогнозом развития аллергического ринита при наличии атопического дерматита (66,67%).
Ключевые слова: *ладонная дерматоглифика, атопический дерматит, бронхиальная астма, аллергический ринит.*

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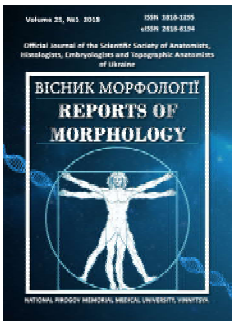

The role of steroid receptors in the pathogenesis of adenomyosis in the presence of concomitant endometrial pathology in postmenopause

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Determining the pathogenesis of adenomyosis in postmenopausal women is promising, as it will allow a more thorough study of the mechanisms of hormonal changes and resolve issues related to adenomyosis in women of reproductive age. The purpose of the study is to establish the role of steroid receptors in the pathogenesis of adenomyosis in the presence of concomitant endometrial pathology in postmenopausal women. Study material is removed uteri with parovaria from 117 patients of 49-76 years old. The cases were divided into 4 groups depending on the presence of adenomyosis (AM) and background pathology (endometrioid carcinoma of the endometrium (ECE) and endometrial hyperplasia (EHP)): 1) 27 women with adenomyosis and EHP; 2) 30 women with adenomyosis and ECE; 3) 30 women with adenomyosis and age-related changes in the endometrium; 4) 30 women with age-related changes without AM (comparison group). The immunohistochemical reaction was carried out using primary antibodies to estrogen (ER), progesterone (PR) and androgen (AR) receptors. Statistical processing was carried out using parametric methods of variation statistics (calculated the arithmetic mean, standard deviation, confidence interval, Student criterion). The predominance of the ER expression in the glandular and stromal components of the eutopic endometrium in the presence of AM and hyperplastic processes was compared with the comparison group ($p<0.01$). A high level of ER expression is characteristic of the epithelium of the endometrium with EHP (7.333±0.314) and ECE (6.200±0.712) rather than for the endometrium with atrophic changes in the presence of AM (4.433±0.773). In the stroma, a high ER activity was detected with EHP (7.148±0.276) rather than with atrophic changes (4.567±0.738) and ECE (4.167±0.602). It was established that in the epithelium of adenomyosis foci, ER expression indices were lower in atrophy (3.433±1.074) than with AM foci in ECE (4.667±0.526) and EHP (5.148±0.745). In the stroma of adenomyosis foci, ER expression is higher in EHP than in ECE and atrophy. The activity of PR in the eutopic endometrium decreases from simple non-typical to complex atypical EHP and in patients with adenomyosis and ECE, as the degree of differentiation of cells of ECA decreases (from G1 to G3 ECE). A minimal expression of PR was found in the comparison group. In the cells of internal endometriosis there were positive indices of immunohistochemical reaction with PR. There were obtained minimum scores for receptor expression of AR in eu- and ectopic endometria. Conclusion: adenomyosis foci have a regulatory effect on the uterine endometrium, stimulating the expression of ER and, to a lesser extent, PR, and do not affect the level of AR in the eutopic endometrium.

Keywords: *adenomyosis, postmenopause, estrogen receptors, progesterone receptors, androgen receptors.*

Introduction

To date, the problem of adenomyosis is urgent and raises many questions from representatives of different medical specialties regarding the methods of diagnosis, the effectiveness of the therapy applied, the prevention of the disease [14, 15, 17, 25, 27].

To address these or other issues related to the specified

pathology, it is necessary to study the features of the pathogenesis of the disease as a key point in the formation of any pathological process. Undoubtedly, hormonal and immunological disorders play a leading role in the development of adenomyosis [8, 9, 23, 24]. In the presence of endometriosis of any localization crucial among all modern methods of examination belongs to morphological research [3, 25]. Determination of immunohistochemical indicators of the expression of eutopic and ectopic endometrial receptors provides an opportunity to understand the mechanisms of emergence and progression of endometrioid disease. There is no single view of the manifestation of the activity of the receptor apparatus of ectopic foci, but the views of all authors agree on one thing: the stromal and epithelial components of the eutopic endometrium in the presence of internal endometriosis differ from that of healthy women in structure, level of activity of processes of proliferation, proliferation, proliferation, proliferation the functioning of the proteolytic system [6, 28]. All known works to study this pathology are aimed at determining the level of expression of receptors of foci of adenomyosis in women of reproductive and premenopausal age [8, 10, 27, 29]. Given the increase in life expectancy, postmenopausal women are more than a third of their lives in this phase [2]. However, the receptor apparatus of the foci of adenomyosis in postmenopausal women and the correlation between eu- and ectopic endometrias remain poorly understood. The study of the problem of adenomyosis in postmenopausal women will allow to study more carefully the complex mechanisms of hormonal changes and their role in the pathogenesis of internal endometriosis, and the greater availability of pathohistological preparations of the removed uterus of this age group allows to study in detail the receptor apparatus and local transformations in the uterus. In addition, in this category of women the range of concomitant pathology of the reproductive system is wider, which certainly influences the development of the disease and may indicate the comorbidity of such diseases [13, 16, 26]. The establishment of separate links in the pathogenesis of adenomyosis, both isolated and in the presence of concomitant endometrial pathology, in post-menopausal women will help address adenomyosis-related issues in women of reproductive age.

All of the above points to the validity of an in-depth comprehensive study of postmenopausal adenomyosis in combination with pathological endometrial processes with the involvement of modern technologies.

The *purpose* of the work is to establish the role of steroid receptors in the pathogenesis of adenomyosis in the presence of concomitant endometrial pathology in postmenopausal women.

Materials and methods

As study material were used removed uterus with appendages from 117 patients 49-76 years old, who were examined and treated at the Center for Reconstructive and Rehabilitation Medicine (University Clinic) of Odessa National Medical University for 2015-2018. Selection criteria - age (postmenopausal - no menstruation for more than a year) and a histologically verified diagnosis of adenomyosis. All cases are divided into 4 groups depending on the presence of AM and on the background pathology (endometrioid endometrial carcinoma (ECE) and endometrial hyperplasia (EHP)): 1) 27 women with adenomyosis and EHP in endometrium; 2) 30 women with adenomyosis and ECE; 3) 30 women with adenomyosis and age-related changes in the endometrium; 4) 30 women with age-related changes without adenomyosis (comparison group).

Table 1. Assessment of the intensity and spread of cell staining as a result of immunohistochemical reaction (points).

Intensity	Distribution of staining
0 = absent 1 = weak 2 = intermediate 3 = strong	(0) - no stained cells (1) - stained cells are less than 1/100 (2) - the number of stained cells from 1/100 to 1/10 (3) - the number of stained cells from 1/10 to 1/3 (4) - the number of stained cells from 1/3 to 2/3 (5) - the number of stained cells is greater than 2/3

Fragments of the test material were fixed in 10 % neutral formalin pH 7.0 for 24 hours at 37°C. Immunohistochemical reaction was performed using primary antibodies: Estrogen Receptor (ER) clone SP1 (titer 1:400, LabVision Corporation, USA), Progesterone Receptor (PR) clone YR85 (titer 1:200, LabVision Corporation, USA), Androgen Receptor (AR) clone AR411 (titer 1:100, Dako, Denmark). The background staining was performed with Mayer's hematoxylin.

The result of immunohistochemical reactions was evaluated by a point system of continuous color method for the determination of ER-, PR-, AR-status according to D.C. Allred et al (1998) (Table 1). The total score was obtained by adding point of staining spread to intensity score. A score of 0 to 2 was considered ER-, PR-, AR-negative, a score > 2 was ER-, PR-, AR-positive.

The grouping, analysis and statistical processing of the obtained data were performed using parametric methods of variational statistics (arithmetic mean, mean error, confidence interval, Student's t-test) and the "Microsoft Office" programs.

Results

Immunohistochemical reactions with ER, PR, AR of the eutopic endometrium in the presence of EHP revealed certain features.

ER and PR showed high mean scores of intensity and prevalence of staining, unlike AR (Table 2). Epithelial cells of eutopic endometrium by EHP in more than a third (44.44 %) of cases were characterized by predominance of ER activity over PR. In the stroma was observed the opposite situation with the predominance of PR over ER.

Immunohistochemical reaction of ER epithelial cells

Table 2. Average intensity and prevalence of staining of ER-, PR-, AR-receptors in eutopic endometrium with EHP (M±m, points).

Material of research	Type of receptor	Glandular component			Stromal component		
		Intensity	Prevalence	Total score	Intensity	Prevalence	Total score
Eutopic endometrium	ER	2.444±0.242	4.889±0.120**	7.333±0.314	2.444±0.191**	4.778±0.160	7.148±0.276
	PR	2.556±0.191*	4.593±0.189***	7.148±0.293	2.815±0.149***	4.482±0.264*	7.296±0.369
	AR	0.815±0.149	1.222±0.283	2.037±0.412	0.704±0.176	0.815±0.235	1.519±0.397
Ectopic endometrium	ER	1.815±0.315	3.444±0.483	5.148±0.745	2.000±0.296	3.482±0.383	5.519±0.640
	PR	2.148±0.250	4.000±0.456	6.148±0.676	2.259±0.307	4.000±0.347	6.259±0.633
	AR	0.333±0.181	0.593±0.335	0.926±0.512	0.630±0.280	0.630±0.280	1.259±0.559

Notes: *- statistically significant differences in ER and PR scores between endometrial components in the group ($p<0.05$); **- statistically significant differences in scores between ER and PR in the group ($p<0.05$); ***- statistically significant differences in scores, both between endometrial components and between ER and PR in the group ($p<0.05$).

Table 3. Average intensity and prevalence of staining of ER-, PR-, and AR-receptors in eutopic endometrium with ECE (M±m, points).

Material of research	Type of receptor	Glandular component			Stromal component		
		Intensity	Prevalence	Total score	Intensity	Prevalence	Total score
Eutopic endometrium	ER	2.367±0.318*	3.833±0.421*	6.200±0.712*	1.400±0.291***	2.767±0.348***	4.167±0.602***
	PR	2.379±0.293	4.000±0.394	6.40±0.656	2.069±0.301**	3.552±0.474**	5.571±0.782**
	AR	0.567±0.224	0.767±0.348	1.333±0.619	0.567±0.180	0.900±0.343	1.467±0.504
Ectopic endometrium	ER	1.667±0.237	3.000±0.339*	4.667±0.526*	1.433±0.243**	2.367±0.493***	3.857±0.621***
	PR	2.000±0.345	3.310±0.507	5.300±0.809	1.931±0.344**	3.241±0.530**	5.32±0.849**
	AR	0.500±0.205	0.900±0.368	1.367±0.598	0.867±0.155	1.400±0.359	2.267±0.479

Notes: *- statistically significant differences in ER and PR scores between endometrial components in the group ($p<0.05$); **- statistically significant differences in scores between ER and PR in the group ($p<0.05$); ***- statistically significant differences in scores, both between endometrial components and between ER and PR in the group ($p<0.05$).

had the highest rates in the centers of adenomyosis with simple EHP without atypia (Fig. 1).

There were no differences in the expression of ER and PR between the components of the ectopic endometrium and between the receptors. AR expression is absent in one third of cases with adenomyosis and EHP. Analysis of the ratio of ER and PR in ectopic endometrium revealed an advantage of expression of PR over ER in more than 40 % of cases.

Among women with G1 ECE, there were more frequent cases with high levels of ER cell gland expression. An opposite situation was observed with G3 ECE, with minimal scores of ER epithelial cell expression.

A similar situation with the expression of ER epithelial cells was observed in the determination of PR expression: maximum indicators of receptor activity - most often for G1 ECE, moderate - for G2 ECE, minimum - for G3 ECE. The latter in some places was characterized by complete absence of immunohistochemical reaction.

The average total ER expression score was not significantly different from such PR (Table 3). AR expression had minimal intensity and color prevalence scores. The study found that the normal distribution of ER and PR, that is, in which the ratio of ER and PR goes to 1, in the glandular component of the eutopic endometrium is present in 13 (43.33 %) women, and in the stromal - only in 8 (26.67 %). In 16 (53.33 %) cases in the stroma, a decrease in ER was observed against the background of an increase in PR (ER/PR<1) ($p<0.05$).

In the ectopic epithelium of ECE, higher scores of ER expression were observed for G1 ECE and minimal and, wherever, complete absence of immunohistochemical reaction for G3 ECE. PR had the highest levels of receptor activity compared to other receptors (Fig. 2).

In the group of patients with adenomyosis and ECE in

Fig. 1. Area of AM female 64 years old with simple EHP without atypia. Expressed IGC reaction (+++) cells glandular (3/5) and stromal components (3/4). IGC reaction to estrogen markers. x100.

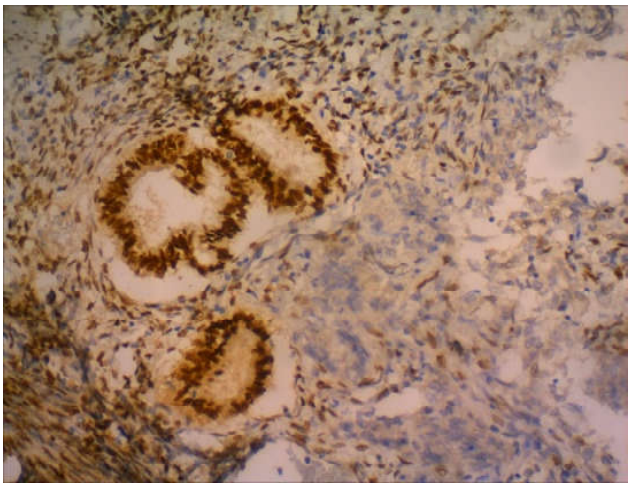

Fig. 2. Area of AM female 66 years in the presence of EKE G2. Pronounced IGC reaction (+++) cells glandular (3/5) and moderate (++) stromal (2/4) components. IGC reaction to estrogen markers. x200.

Fig. 3. Area of AM female 62 years old with endometrial atrophy. Expressed IGC reaction (+++) cells of the glandular (3/5) and stromal (3/5) components. IGC reaction to markers of progesterone. x100.

Table 4. Average intensity and prevalence of staining of ER-, PR-, AR-receptors in eutopic endometrium with atrophy (M±m, points).

Material of research	Type of receptor	Glandular component			Stromal component		
		Intensity	Prevalence	Total score	Intensity	Prevalence	Total score
Eutopic endometrium	ER	1.467±0.244	2.967±0.544	4.433±0.773	1.700±0.328	2.833±0.432	4.567±0.738
	PR	1.800±0.317	3.367±0.613	5.167±0.907	2.000±0.364	3.467±0.585	5.467±0.943
	AR	0.367±0.175	0.767±0.406	1.133±0.570	0.667±0.368	0.667±0.4368	1.33±0.736
Ectopic endometrium	ER	1.233±0.384**	2.200±0.700**	3.433±1.074**	1.700±0.341**	2.733±0.469**	4.433±0.790**
	PR	2.200±0.288**	3.967±0.425**	6.167±0.704**	2.400±0.276**	3.733±0.338**	6.167±0.595**
	AR	0.333±0.172	0.667±0.391	1.0±0.548	0.967±0.318	1.400±0.511	2.367±0.816

Notes: **- statistically significant differences in scores between ER and PR in the group ($p<0.05$).

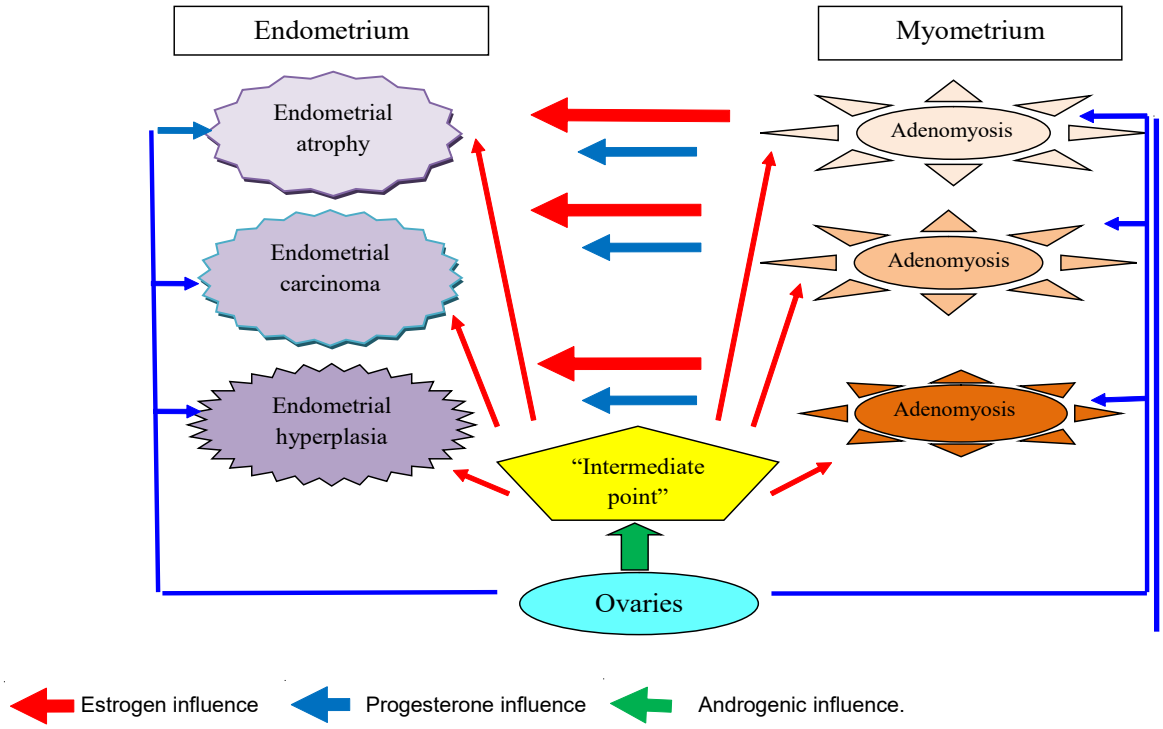

Fig. 4. Scheme of pathogenesis of adenomyosis in postmenopausal women.

Table 5. Average intensity and prevalence of staining of ER-, PR-, and AR-receptors in endometrium with age-related changes (M±m, points).

Type of receptor	Glandular component			Stromal component		
	Intensity	Prevalence	Total score	Intensity	Prevalence	Total score
ER	0.967±0.318	1.567±0.577	2.533±0.885	0.767±0.261	1.500±0.513	2.267±0.757
PR	1.100±0.391	1.900±0.589	3.000±0.968	1.000±0.282	2.100±0.590	3.100±0.858
AR	0.833±0.327	1.37±0.598	2.200±0.918	0.533±0.308	0.667±0.431	1.200±0.718

the stroma, there is a higher level of PR expression than ER, in contrast to the glandular component (Table 3). Immunohistochemical reaction with AR in glandular cells was more often absent, in stroma - had minimal indicators of receptor expression. All patients showed a predominance of ER over PR in the stroma of endometrioid heterotopias ($p<0.05$).

There were no differences in the expression of ER and PR in the group with AM and endometrial atrophy between the components of the eutopic and between the receptors themselves (Table 4). The intensity and prevalence of AR coloration in most women were zero.

In 19 (63.33%) women of group III in epithelial cells of eutopic endometrium the predominance of the ratio ER/PR=1 ($p<0.05$) was established. In the stroma, there was a more frequent decrease in ER relative to PR (ER/PR<1) ($p<0.05$).

In ectopic endometrium in atrophy in one third of women with IGC, the response of ER glandular cells was absent. Immunohistochemical reaction of PR in more than one third of cases was evaluated in maximum parameters (Fig. 3), unlike AR. The prevalence of PR expression over ER in the foci of adenomyosis was established ($p<0.05$) (Table 4).

The glandular component of the ectopic endometrium in most women was characterized by an increase in PR and a decrease in ER (EP/PR<1) ($p<0.05$). A similar pattern with a predominance of PR was also found in stroma cells ($p<0.05$) (Fig. 4).

Immunohistochemical study of the receptor apparatus of glandular and stromal cells of the endometrial women of the comparison group to markers ER, PR and AR revealed minimal scores in both intensity and prevalence of staining (Table 5).

Discussion

Speaking about the overall picture of the results of the study, postmenopausal patients are characterized by differences in the expression levels of ER, PR, and AR not only between the components of the eu- and ectopic endometrium of the respective groups, but also between the groups themselves.

The presence of high rates of ER activity in endometrial components of EHP confirms the role of hyperestrogenemia in the pathogenesis of EHP. Endometrial cell proliferation is facilitated by long-term estrogen exposure [1, 7, 8, 17, 21]. The steroid dependence of endometrial glandular cells on EHP is undeniable. Stromal cells also exhibit positive ER activity, as confirmed by the work of other scientists [7, 11, 21].

The highest rates of ER expression in the stroma of the eutopic endometrium with EHP were observed in simple and complex forms of EHP without atypia. Atypical - immunohistochemical reaction was less pronounced and was accompanied by a decrease in ER expression, indicating a violation of their reception. According to V.O. Beniuk and co-authors (2013), decrease in the level of activity of the receptor apparatus indicates the worsening of the pathological process and the likelihood of further malignancy [7]. According to the works of Tumansky V.O. and Baudarbekova M.M. (2009), pronounced ER activity was found in non-atypical EHP, moderate and weak in atypical EHP [21]. The opposite is the opinion of Z.V. Chumak et al (2014): atypical EHP is characterized by higher ER expression results than non-atypical EHP. However, all of the above results were relevant for women of predominantly reproductive and premenopausal age [11].

Analysis of the results of estrogen receptor expression in eutopic endometrium with endometrioid endometrial carcinoma revealed an increase in receptor activity from G3 to G1 ECE, which is in line with the O.A. Samsonova data (2004) on the more frequent detection of estrogen and progesterone receptors in highly differentiated endometrial tumors and a decrease in their activity and quantity in accordance with a decrease in the degree of cell differentiation [20]. Decrease in the expression of ER, or lack thereof, indicate a loss of regulatory effect of estrogen hormones and autonomic growth of the tumor process [8, 22].

Positive expression of ER eutopic endometrium was detected in the presence of atrophy and adenomyosis, which indicates the preservation of receptor activity and regulatory influence of postmenopausal estrogens in the absence of hyperplastic processes in the endometrium.

Analysis of the results of immunohistochemical reactions in the endometrium of women in the comparison group showed low hormonal dependence of endometrial components, as indicated by the minimal scores of ER expression of glandular and stromal cells.

The study found a predominance of the expression level of ER in the glandular and stromal components of the eutopic endometrium in the presence of adenomyosis and hyperplastic processes compared with the comparison

group (p<0.01). The obtained data partly correspond to the results of other scientists. So, V.O. Beniuk et al. (2013), although it is claimed that the content of ER in epithelial cells of endometrium with EHP is higher than in women without the specified pathology, but in the stroma of reliable differences scientists have not established [7]. The presence of lower intensity scores and the spread of ER staining in the stromal component, compared with the glandular (p<0.05), indicates an uneven effect of the same hormones on the respective structures and their different hormonal dependence. Tumansky V.O. and Chepetz A.V. (2016) holds the same opinion., indicating a decrease in ER expression in stroma cells compared with gland cells [22].

The results show that higher expression of ER is characteristic of epithelial cells in endometrium with EHP (7.333±0.314 points) and ECE (6.200±0.712 points) than in endometrium with atrophic changes in the presence of adenomyosis (4.433±0.773 points). In stromal cells, higher ER activity rates were detected by EHP (7.148±0.276 points) compared to endometrium with atrophic changes (4.567±0.738 points) and ECE (4.167±0.602 points).

Positive immunohistochemical reaction from ER components of endometrioid heterotopias in postmenopausal women indicates the hormonal dependence of pathological foci and the key role of steroid hormones in the development and conservation of foci of adenomyosis. The study found positive overall cumulative ER reception in all groups of women with adenomyosis. R.A. Akopyan and V.A. Pechenikova (2014), O.G. Kuryk and O.V. Kalenska (2014) indicated positive expression of ER in endometrioid foci [4, 18]. Some authors have suggested that estrogen levels increase locally in postmenopausal women with internal endometriosis, but these studies have addressed patients with isolated pathology - adenomyosis [4]. Other scientists have emphasized the leading role in the development of "hyperplastic syndrome" (EHP, adenomyosis and uterine fibroids) of local hyperestrogenemia, not balanced by hyperprogesteronemia [17]. Local hyperestrogenemia may be the result of local hormone synthesis, indicating the autonomy of endometrioid foci [7].

It was found that in the glandular component of internal endometriosis foci, lower ER expression was observed in atrophy (3.433±1.074 points) compared to foci of adenomyosis in endometrioid carcinoma (4.667±0.526 points) and endometrial hyperplasia (5.148±0.745). In endometrioid heterotopy stroma, estrogen receptor expression is higher in hyperplasia than in endometrioid endometrial carcinoma and atrophy.

When comparing the results of the expressive activity of the steroid receptors of the eu- and ectopic endometrium, no differences were found (p>0.05), except for the group of women with adenomyosis and EHP. The data obtained differ with the findings of some studies, according to which the level of ER in the traces of endometrioid heterotopias is lower than in eutopic endometrium [7, 30]. Patients with adenomyosis and endometrial hyperplasia have a predominance of ER expression over PR in eutopic endometrium (p<0.01). This situation can be explained as follows: endometrioid foci have some estrogenic potential, which in turn affects the eutopic endometrium. Such dependence is confirmed by the fact of lower expressive ER activity in the endometrium of the comparison group relative to the eutopic endometrium in the group of patients with atrophy and adenomyosis, both in the stroma and in the glands. The following pattern is interesting: the higher the estrogenic potential of the eutopic endometrium, the higher the ER expression in endometrioid foci. This phenomenon is well evident in the group with endometrioid endometrial carcinoma, since in this group there were patients, depending on the level of cell differentiation, with both high and low estrogen receptor expression scores in the eutopic endometrium. The higher the level of differentiation of ECE cells, the higher was the estrogenic activity in the endometrium of ECE and in the focuses of internal endometrosis. This is evidenced by higher scores of ER expression in AM focuses on EHP than in atrophy, in which the eutopic endometrium has lower estrogen activity rates.

The cells of the components of the eu- and ectopic endometrium have estrogenic and progesterone activity, which coincides with the conclusions reached in their work in 2014 by R.A. Hakobyan and V.A. Pechenikova, and O.G. Kuryk and O.V. Kalenskaya [4, 18]. Progesterone receptors have no less activity than estrogen in endometrium with endometrial hyperplasia, and, in some cases, even greater [21]. The activity of PR decreases from simple non-atypical to complex atypical EHP [11].

In patients with adenomyosis and endometrioid carcinoma of the endometrium observed a similar pattern with the expression of PR, as for estrogen receptors: as the degree of differentiation of ECE cells (from G1 to G3 ECE) decreased the receptor activity of progesterone receptors. Reduction of PR expression or their absence in ECE cells V.A. Tumansky and A.V. Chepetz in 2016 explained the loss of regulatory influence of steroid hormones and the autonomy of tumor growth [22].

In the comparison group, minimal PR expression indicated low hormonal dependence of endometrial components in women without adenomyosis and postmenopausal endometrial hyperplastic processes.

Positive PR expression in internal endometriosis cells was found in groups of women with adenomyosis, which proves their hormonal dependence and the key role of these hormones in the existence of postmenopausal focuses of adenomyosis. It is possible that this is a consequence of the local synthesis of progesterone hormones in endometrioid foci [4]. Cases with low activity and moderate expression of PR are associated with a decrease in progesterone dependence.

When comparing the expression scores of steroid receptors of the eu- and ectopic endometrium, no differences were found between the indices (p>0.05). An exception was women with adenomyosis and EHP, which was dominated

by expression of progesterone receptors in eutopic endometrial cells over ectopic (p<0.01). Thus, the results obtained are partly consistent with the findings of some scientists, according to which the level of progesterone receptors in the foci of adenomyosis is lower than in the eutopic endometrium [4, 30].

The preservation of the expression of the PR foci of postmenopausal adenomyosis in both epithelial and stromal cells was confirmed, regardless of concomitant pathology. However, there were no significant differences between the mean total PR expression scores in the stroma of ectopic foci. This indicates the absence of regularities between the expression levels of PR eu- and ectopic endometrium, depending on the level of cell differentiation inherent in estrogen receptors. It should be noted that PR activity differed in eutopic endometrium depending on the presence of internal endometriosis. Patients with atrophy and adenomyosis had higher progesterone receptor expression scores in eutopic endometrium than the comparison group women. Endometrioid foci may have a regulatory effect on eutopic endometrium, with some progesterone potential. However, they remain independent of the eutopic endometrial feedback.

When comparing the expression of ER and PR revealed both the normal ratio of ER and PR, and the predominance of ER over PR, as evidenced by the presence of only 2 phenotypic variants of the distribution of receptors ER and PR: ER>PR and ER=PR. The advantage of ER over PR in non-atypical EHP in their study was established by V.O. Tumansky and M.M. Baudarbekova (2009) [21]. According to the work of V.O. Beniuk and V.M. Goncharenko (2013), just enough receptors for progesterone and maintaining a normal ratio of ER and PR, which goes to 1, provides sensitivity of the endometrium with EHP to progestin therapy [8]. Thus, not only hyperestrogenemia, but also hyperprogesteronemia and maintaining the appropriate ratio of ER and PR are important in the pathogenesis of simple atypical EHP. Therefore, not only the ER but also the level of PR plays a leading role in proliferative processes in the endometrium. The transition of the non-atypical form to the atypical one is accompanied not only by a decrease in the sensitivity of the receptor apparatus, but also by the predominance of progesterone receptors over estrogenic ones.

The presence of more than 60 % of women with adenomyosis and atrophy in epithelial cells in the eutopic endometrium of a normal ratio of ER and PR, which went to 1 (p<0.05), indicates that the condition of the existence of glandular elements of eutopic endometrium with adenomyosis and without hyperplastic processes are to maintain a balance between ER and PR. The situation is different when was observed in stromal cells: in most cases there was a decrease in estrogen receptors against a background of progesterone increase (ER/PR<1) (p<0.05). This indicates the advantage of progesterone exposure.

In the group of women with adenomyosis and ECE it was found that the stroma showed higher expression of PR than ER (p<0.05). This indicates a greater regulatory effect of progesterone receptors than estrogen receptors. It was in the stroma of the endometrium with ECE that a decrease in ER was observed against the background of an increase in PR (ER/PR<1) (p<0.05). In the epithelial cells of the ectopic endometrium, ECE was dominated by a balanced variant of the ratio ER and PR (ER=PR) (p<0.05). Higher PR expression in the stroma demonstrates progesterone dependence of endometrioid heterotopia cells and indicates its superiority over estrogen. This is confirmed by the smaller number of cases (6.67 %) with the phenotypic variant of receptor distribution in the stroma foci AM - ER/PR>1 (p<0.05). Other scientists point to the positive expression of PR in endometrioid heterotopias in women of both reproductive and menopausal periods [4, 18, 19].

In women with adenomyosis and endometrial atrophy the opposite situation was observed: in endometrioid foci, the expression of PR was higher than ER (p<0.05), and in most cases there was a phenotypic variant of the ratio of receptors with a predominance of PR over ER (EP/PR<1) (p<0.05). Therefore, for postmenopausal adenomyosis pathogenetically important is the advantage of progesterone influence over estrogen.

Different levels of receptors under study at foci of adenomyosis result from different hormonal dependence of endometrioid focus cells. For the development and existence of internal endometriosis in postmenopausal sufficient estrogen and progesterone effects are required. The implementation of the cellular response is a consequence of the interaction of the hormone and the corresponding receptor. In postmenopausal conditions, a sufficient number of hormones can be synthesized locally, in the foci of adenomyosis, against the background of the ovarian function. However, it should not be forgotten that in groups of women, adenomyosis "coexisted" with EHP and ECE, whose endometrium had some hormonal potential and receptor activity. Therefore, in the pathogenesis of postmenopausal adenomyosis, local estrogen and progesterone activities of constituent ectopic foci play a leading role.

The study obtained minimal indicators, and sometimes complete absence, of AR receptor expression in the eu- and ectopic endometriums, which indicates that there is no direct regulatory effect on the development of androgen adenomyosis. However, despite this, AR expression in stromal ECE is higher in focal endometriosis foci than in eutopic endometrium (p<0.05). In the analysis of the activity of AR differences between the expression levels in the eutopic endometrium of the studied groups of women were not found, which suggests that the androgenic potential of foci of adenomyosis and their influence on the level of AR in the eutopic endometrium is absent.

Evaluation of the results of AR expression in ectopic endometrium showed the presence of lower rates of AR expression in the stroma of endometrioid foci on EHP

compared with other patients in the study group ($p<0.05$). However, the level of AR activity in all study groups was minimal.

Some researchers, studying the peculiarities of the existence of post-menopausal EHP, argue that this is possible in the presence of hormone-active structures in the ovaries and extra-gonad synthesis of estrogens in adipose tissue or inflammatory processes of the endometrium and appendages of the uterus [12]. Since the leading role in the pathogenesis of adenomyosis and EHP is played by local hyperestrogenemia, these pathological conditions can cause the development of adenomyosis. Given the possibility of estrogen synthesis in focal endometriosis foci, endometrioid heterotopias can be considered as an autonomous lesion of the myometrium and a source of estrogen synthesis for eutopic endometrium. This hypothesis is confirmed by the presence of higher rates of ER expression in eutopic endometrium in the presence of adenomyosis, including atrophic changes than in women without adenomyosis. The absence of estrogenic potential of the ovaries in postmenopausal women, positive expression of ER in the eu- and ectopic endometriums may indicate the existence of an "intermediate point" of estrogen synthesis. In the future, the estrogens synthesized at such an intermediate point are sent to the eu- and ectopic endometrium. Estrogens that have reached the foci of adenomyosis potentiate greater estrogen production in endometrioid heterotopias. Subsequently, some of the estrogens remain in the focuses of adenomyosis, and some go to the eutopic endometrium. Thus, the hormonal theory of the pathogenesis of adenomyosis, which is the basis of hyperestrogenia, is inferior to the theory of hormonal metabolism disorders, based on impaired sensitivity of hormone-dependent tissues to the influence of steroids and pronounced imbalance of estrogens, progesterone and androgens.

To summarize, we can propose the following concept of pathogenesis of postmenopausal adenomyosis. Estrogens, formed at the "intermediate point" of androgens, affect the eu- and ectopic endometrium. Endometrioid foci (as an autonomous system), in turn, stimulate the presence of positive estrogen and, to a lesser extent, progesterone expression in the eutopic endometrium (Fig. 4).

Prospects for further development are to study the eutopic endometrium and foci of internal endometriosis of the expression of P-450 aromatase, as a possible key enzyme under which the formation of estrogens from androgens takes place.

Conclusions

1. Higher levels of differentiation of eutopic endometrial cells correspond to higher estrogenic activity of eu- and ectopic endometrium. Focuses of adenomyosis affect the eutopic endometrium, stimulating the activity of ER.

2. Endometrioid foci exert a regulatory effect on eutopic endometrium in the form of PR stimulation. Adenomyosis foci remain independent of the eutopic endometrium feedback.

3. The absence of androgenic potential of foci of adenomyosis and their influence on the level of AR in eutopic endometrium were revealed.

4. We suggest to consider endometrioid foci as an autonomous source of production of estrogen and progesterone hormones. Adenomyosis foci stimulate the presence of positive estrogen and, to a lesser extent, progesterone expression in the eutopic endometrium.

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РОЛЬ СТЕРОЇДНИХ РЕЦЕПТОРІВ У ПАТОГЕНЕЗІ АДЕНОМІОЗУ ЗА НАЯВНОСТІ СУПУТНЬОЇ ПАТОЛОГІЇ ЕНДОМЕТРІЯ В ПОСТМЕНОПАУЗІ

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Встановлення ланок патогенезу аденоміозу у жінок в постменопаузі є перспективним дослідженням, яке дозволить ретельніше вивчити механізми гормональних змін і вирішити питання, пов'язані з аденоміозом у жінок репродуктивного віку. Мета роботи - встановити роль стероїдних рецепторів у патогенезі аденоміозу за наявності супутньої патології ендометрія в постменопаузі. Матеріалом для дослідження були матки, видалені з придатками, 117 пацієнток віком від 49 до 76 років. Всі пацієнтки були розділені на 4 групи залежно від наявності аденоміозу та фонової патології (ендометріоїдна карцинома ендометрія (ЕКЕ) і гіперплазія ендометрія (ГПЕ)): 1) 27 жінок з аденоміозом і ГПЕ; 2) 30 жінок з аденоміозом та ЕКЕ; 3) 30 жінок з аденоміозом та віковими змінами в ендометрії; 4) 30 жінок з віковими змінами без аденоміозу (група порівняння). Імуногістохімічну реакцію проводили з використанням первинних антитіл до естрогенових (ER), прогестеронових (PR) і андрогенових (AR) рецепторів. Статистичну обробку проводили із застосуванням параметричних методів варіаційної статистики (вираховували середнє арифметичне, стандартне відхилення, довірчий інтервал, критерій Стьюдента). Встановлено переважання рівня експресії ER у залозистому і стромальному компонентах еутопічного ендометрія за наявності аденоміозу і гіперпластичних процесів порівняно з групою порівняння (p<0,01). Вищий рівень експресії естрогенових рецепторів був більш характерним для епітелія ендометрія з гіперплазією (7,333±0,314) та ендометріоїдною карциномою

(6,200±0,712), ніж для ендометрія з атрофічними змінами при аденоміозі (4,433±0,773). Більш висока активність естрогенових рецепторів у стромі виявлена при гіперплазії ендометрія (7,148±0,276), ніж при атрофічних змінах (4,567±0,738) та ендометріоїдній карциномі (4,167±0,602). Встановлено, що в епітелії вогнищ аденоміозу при атрофії експресія естрогенових рецепторів були нижчою (3,433±1,074), ніж у фокусах аденоміозу при ендометріоїдній карциномі ендометрія (4,667±0,526) та його гіперплазії (5,148±0,745). У стромі фокусів аденоміозу експресія естрогенових рецепторів вища при гіперплазії ендометрія, ніж при ендометріоїдній карциномі ендометрія та атрофії. Активність прогестеронових рецепторів в еутопічному ендометрії знижується від простої неатипової до комплексної атипової гіперплазії ендометрія, а у пацієнток з аденоміозом та ендометріоїдною карциномою ендометрія - по мірі зниження ступеню диференціації клітин ЕКЕ (від G1 до G3 ЕКЕ). У групі порівняння виявлена мінімальна експресія прогестеронових рецепторів. У клітинах внутрішнього ендометріоза наявні позитивні показники імуногістохімічної реакції з PR. Отримані мінімальні бали рецепторної експресії андрогенових рецепторів в еу- та ектопічному ендометрії. Таким чином, фокуси аденоміозу здійснюють регуляторний вплив на еутопічний ендометрій, стимулюючи експресію естрогенових рецепторів і, в меншій мірі, прогестеронових рецепторів, і не впливають на рівень андрогенових рецепторів в еутопічному ендометрії.

Ключові слова: *аденоміоз, постменопауза, естрогенові рецептори, прогестеронові рецептори, андрогенові рецептори.*

РОЛЬ СТЕРОИДНЫХ РЕЦЕПТОРОВ В ПАТОГЕНЕЗЕ АДЕНОМИОЗА ПРИ НАЛИЧИИ СОПУТСТВУЮЩЕЙ ПАТОЛОГИИ ЭНДОМЕТРИЯ В ПОСТМЕНОПАУЗЕ

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Определение звеньев патогенеза аденомиоза у женщин в постменопаузе является перспективным исследованием, которое позволит более тщательно изучить механизмы гормональных изменений и решить вопросы, связанные с аденомиозом у женщин репродуктивного возраста. Цель исследования - установить роль стероидных рецепторов в патогенезе аденомиоза при наличии сопутствующей патологии эндометрия в постменопаузе. Материалом для исследования служили матки, удаленные с придатками, 117 пациенток в возрасте 49-76 лет. Все пациентки были разделены на 4 группы в зависимости от наличия аденомиоза и фоновой патологии (эндометриоидная карцинома эндометрия (ЭКЭ) и гиперплазия эндометрия (ГПЭ)): 1) 27 женщин с аденомиозом и ГПЭ; 2) 30 женщин с аденомиозом и ЭКЭ; 3) 30 женщин с аденомиозом и возрастными изменениями в эндометрии; 4) 30 женщин с возрастными изменениями без аденомиоза (группа сравнения). Иммуногистохимическую реакцию проводили с использованием первичных антител к эстрогеновым (ER), прогестероновым (PR) и андрогеновым (AR) рецепторам. Статистическую обработку проводили с применением параметрических методов вариационной статистики (вычисляли среднее арифметическое, стандартное отклонение, доверительный интервал, критерий Стьюдента). Установлено преобладание уровня экспрессии эстрогеновых рецепторов в железистом и стромальных компонентах эутопического эндометрия при наличии аденомиоза и гиперпластических процессов по сравнению с группой сравнения (p<0,01). Высший уровень экспрессии эстрогеновых рецепторов был более характерен для эпителия эндометрия с гиперплазией (7,333±0,314) и эндометриоидной карциномой эндометрия (6,20±0,712), чем для эндометрия с атрофическими изменениями при наличии аденомиоза (4,433±0,773). В строме более высокая активность ER обнаружена при гиперплазии эндометрия (7,148±0,276), чем при атрофических изменениях (4,567±0,738) и ЭКЭ (4,167±0,602). Установлено, что в эпителии очагов аденомиоза ниже показатели экспрессии эстрогеновых рецепторов были при атрофии (3,433±1,074), чем в фокусах аденомиоза при эндометриоидной карциноме (4,667±0,526) и гиперплазии эндометрия (5,148±0,745). В строме фокусов аденомиоза экспрессия эстрогеновых рецепторов выше при гиперплазии эндометрия, чем при эндометриоидной карциноме эндометрия и атрофии. Активность PR в эутопическом эндометрии снижается от простой неатипичной к комплексной атипичной ГПЭ, а у пациенток с аденомиозом и эндометриоидной карциномой эндометрия - по мере снижения степени дифференциации клеток ЭКЭ (от G1 до G3 ЭКЭ). В группе сравнения обнаружена минимальная экспрессия PR. В клетках внутреннего эндометриоза присутствовали положительные показатели иммуногистохимической реакции с PR. Получены минимальные баллы рецепторной экспрессии AR в эу- и эктопическом эндометриях. Таким образом, фокусы аденомиоза осуществляют регуляторное влияние на эутопический эндометрий, стимулируя экспрессию ER и, в меньшей степени, PR, и не влияют на уровень AR в эутопическом эндометрии.

Ключевые слова: *аденомиоз, постменопауза, эстрогеновые рецепторы, прогестероновые рецепторы, андрогеновые рецепторы.*

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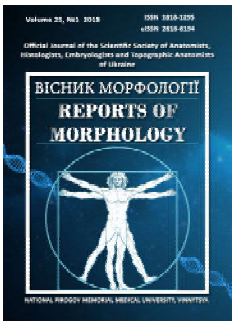

Structural changes of duodenal mucosa enterocytes of rats in burn skin injury under experimental streptozotocin-induced diabetes mellitus

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The work is devoted to the study of structural changes of enterocytes in the mucous membrane of the duodenum in a burn injury of the skin of a rat under conditions of experimental streptozotocin induced diabetes. The study was carried out on laboratory white adult rats-males weighing 180-210 g. The control group consisted of 21 animals without somatic pathology, the first experimental group consisted of 21 rats with skin burn injury, the second experimental group cleared 21 rats with skin burn and experimental streptozotocin induced diabetes. A model of experimental diabetes mellitus was reproduced by administering streptozotocin intraperitoneally once in dose of 50 mg/kg to rats. In an experimental simulation of a skin burn, two copper plates in the form of an ellipse were kept in water at 100°C for 10 minutes and, under ether anesthesia conditions, were applied simultaneously symmetrically on both exposed parts of the body of rats with an exposure for 10 seconds. Burn skin damage in rats was II-AB degrees - dermal surface burn (according to the old classification III-A degree) with a total area of 21-23% of the body surface with the development of burn shock. For morphological studies, the duodenum was taken, fragments of which were processed using conventional light and electron microscopy. The main criteria for assessing damage the enterocytes of the duodenal mucosa were the results studies of histological and ultrastructural data over 7, 14 and 21 days after a skin burn. The results of the studies showed that the damage of the enterocytes of the duodenal mucosa is based on deep destructive changes, which after 21 days (at the stage of septic toxemia), as a rule, are not reversible and develop against the background of significant intoxication of the organism. In the mucous membrane of the duodenum with burn injury of the skin associated with diabetes mellitus, there is a deterioration of the manifestations of the adaptive response and prolongation of destructive processes, accompanied by a violation of intercellular interactions in cytoarchitectically modified and deformed villi and crypts.
Keywords: *burn injury, streptozotocin-induced diabetes mellitus, morphological changes of the duodenum.*

Introduction

In modern conditions of intensive industrialization and more increasing growing worldwide use of heat sources in everyday life, there is an increase in the frequency of burn traumatic injuries [10, 12, 13, 14, 18, 20]. Deep widespread burns are characterized not only by damage to the integumentary tissues, but also cause burn disease, which is characterized by different, lasting and peculiar general morphological and functional changes of all organs and systems of the organism [16]. It is clear that burn injury of the skin causes significant changes, first of all, skin cells [15], but damage to the skin is considered to be the main pathogenic mechanism that causes the development of burn disease, the components and factors of which are: generalized catabolic response in the trauma center and in all internal organs, systemic inflammatory and apoptotic responses, endogenous intoxication and multiple organ dysfunction [3, 8, 9].

Particularly unfavorable is the course of burn disease in the context of its association with diabetes mellitus [6, 16]. However, structural changes enterocytes of the mucous

membrane duodenum the conditions of association burn disease with diabetes have so far remained unheeded by researchers. On this basis, the important role of duodenal dysfunction in the pathogenesis of burn disease [4, 6] determines the need to study the morphogenesis of destructive and regenerative processes in its mucous membrane at different times after burn injury under the conditions of the course of diabetes mellitus.

The purpose of the work was to study the structural changes of enterocytes in the mucous membrane of the duodenum in burn injury of the skin of rats under the conditions of experimental streptozotocin-induced diabetes mellitus.

Materials and methods

This research was conducted on laboratory white adult male rats weight 180-210 g. The control group consisted of 21 animals without somatic pathology, the first experimental group consisted of 21 rats with burn skin injury, the second experimental group consisted of 21 rats with skin burn and experimental streptozotocin-induced diabetes. All studies and control of the animals were conducted in accordance with the rules for the use of the animals in the experiments, adopted by the "European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes" (Strasbourg, 1986), "General Ethica Principles of Animal Experiments", adopted by the First National Congress On Bioethics (Kyiv, 2001), "Ethical Principles and Guidelines for Experiments on Animals: 3rd Edition" (Switzerland 2005) and the Law of Ukraine "On the Protection of Animals from Cruel Treatment" (2006). The experimental diabetes model was reproduced by administering streptozotocin to the rats intraperitoneally at a dose of 50 mg/kg, pre-dissolving it in 0.1M citrate buffer solution (pH-4,5). The duration of the experiment was 1 month. The control of the development of hyperglycemia in the second experimental group was blood glucose level - 24.24±0.79 mmol/L. In the control group 8.03±0.4 mmol/L.

In our research, burn skin injury was caused in accordance with the widespread model among researchers Regas F.C. and Ehrlich H.P. [17], which has been slightly modified and optimized Gunas I.V. with co-authors [7]. In the experimental simulation of skin burns, two copper plates in the form of an ellipse were kept in water at 100 ° C for 10 minutes and, under the conditions of ether anesthesia, were simultaneously applied symmetrically to both exposed rats with an exposure of 10 seconds. Burn skin damage in rats was IIA-B grade - dermal surface burn (according to the old classification IIIA grade) with a total area of 21-23% of the body surface with the development of burn shock. For morphological research the department of the duodenum was selected, a fragment of which was processed by conventional methods of light and electron microscopy. Semi-thin and ultrathin sections from epoxy blocks were obtained on an LKB ultratome (Sweden). Ultra-thin sections after appropriate contrast were examined under a PEM-125K electron microscope. Semi-thin sections were stained with methylene and toluidine blue. Sections of paraffin blocks were stained with hematoxylin-eosin.

The main criteria for assessing damage enterocytes of the mucous membrane duodenum were the results of histological and ultrastructural data in dynamics after 7, 14, and 21 days after skin burns. Within the specified time rats were injected a single intraperitoneally large dose of sodium thiopental and removed from the experiment by decapitation.

Results

In the duodenum mucous membrane of the animals of the first experimental group 7 days after burn found dystrophic changes in most enterocytes while maintaining the shape of unevenly swollen and infiltrated by lymphocytes (as well as leukocytes) villi (Fig. 1). Columnar borderless enterocytes, goblet cells, and intestinal

Fig. 1. Leukocyte and lymphocytic infiltration of the swollen villi of the duodenal mucosa of the first experimental group 7 days after burn. Hematoxylin-eosin. x60.

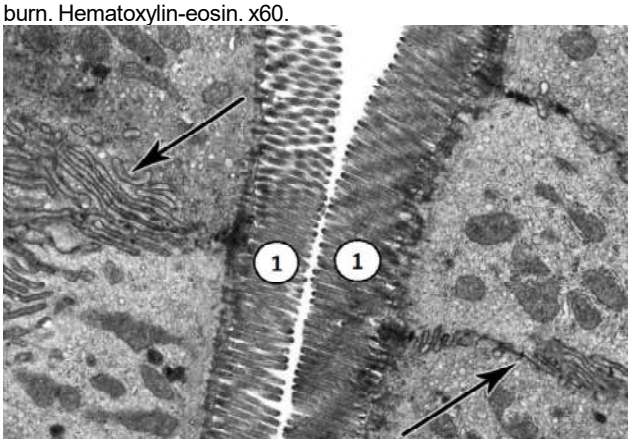

Fig. 2. Ultrastructural organization of enterocytes with a brush border in the mucous membrane of the duodenum of the rat under normal conditions (control group of animals). The arrows indicate the inter-digitization of the cytoplasmic processes of adjacent enterocytes. 1 - brush border. EM x10000.

endocrinocytes were simultaneously altered. The described changes in the epithelial lining were accompanied by the expansion of the interepithelial spaces. These extensions revealed interepithelial lymphocytes, which also had pronounced damage to the structure. These morphological sings of the epithelial monolayer are significantly different from those under normal conditions.

In animals of the control group (Fig. 2), the apical portion of each columnar enterocyte with a brush border contains monofilaments, by means of which is formed dense intercellular contacts that isolate the lateral surface of enterocytes from the contents of the intestinal lumen. The cytoplasm of adjacent enterocytes has long thin processes that form interdigitations of complex shape along the contacting lateral surfaces of cells. Due to the availability of dense contacts and interdigitation of cytoplasmic processes, the maximum convergence of plasmalemma of adjacent enterocytes is ensured and the maximal decrease intercellular spaces in the epithelium. Under the conditions of preservation of the integrity of the epithelial monolayer, a characteristic single-type, saved mainly leaf-like form of the villi of the mucous membrane duodenum.

In the mucous membrane of the duodenum of the animals of the first experimental group 7 days after burn, concomitant changes in the microcirculatory bed caused perivasal edema, leukocyte infiltration, diapedesis of erythrocytes, rupture of individual micro vessels with the formation of hemorrhages. In comparative analysis of the structural organization of the mucosa of the duodenum in this group of animals observed manifestations of adaptive processes. Detected the availability of a more pronounced folding of the mucous membrane. The villi are well developed, thickened, their own lamina includes a considerable number of lymphocytes.

Widespread phenomenon in this time interval is a variety of ultrastructural changes of enterocytes against the background of swelling of their cytoplasm (an indicator of which is the enlightenment of the cytoplasmic matrix): from the vacuolation of the tubules of the endoplasmic reticulum and damage to the mitochondria (manifestation is their intense swelling, fragmentation of the crust and inner membrane), to the complete destruction of organelles, the appearance of defects of plasmalemma and nuclear membrane.

In areas of enterocytes cytoplasm with partially lost brush border there are rounded autophagosomes and autophagolysosomes of different size with heteromorphic electron-dense contents (Fig. 3).

Morphological evidence of the initial stage of autophagy is the grouping of damaged cell organelles in certain loci of the cytoplasmic matrix and their sequestration by concentric coverage of the characteristic autophagosome structure - phagophore (double insulating membrane). In the future, autophagosomes merge with lysosomes and form autophagosomes with different electron density and structure (which is an indicator of the stages and efficiency

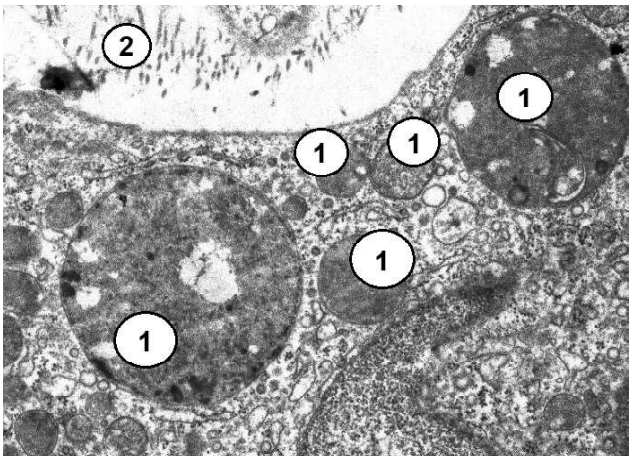

Fig. 3. Autophagosomes (1) of various sizes with heteromorphic electron-dense contents in the cytoplasm of enterocyte with the remnants of the brush border in the mucous membrane of the duodenum of the rat of the first experimental group 7 days after burn, 2 - the remnants of the brush border. EM x20000.

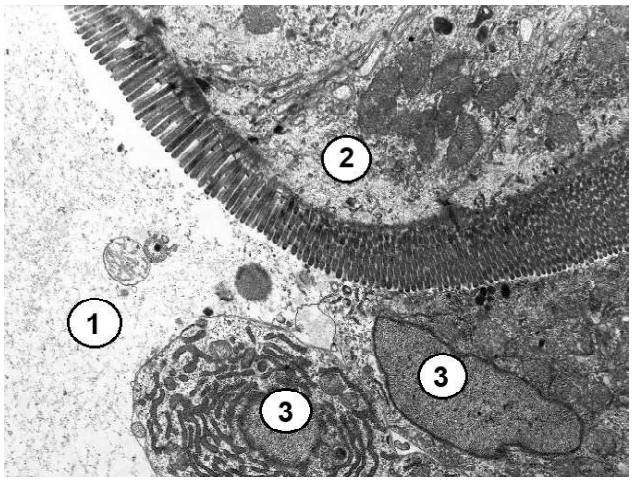

Fig. 4. Area of epithelial monolayer of enterocytes with preserved brush border and desquamated cells in the margins in the mucous membrane of the duodenum of the rat of the first experimental group 14 days after burn. 1 - intestinal lumen, 2 - cytoplasm of enterocyte with brush border, 3 - the nucleus of the desquamated cell. EM x10000.

of digestion of the sequestered material).

Digestion of the content of autophagolysosomes is accompanied by destruction of the inner membrane of the phagophore (under these conditions, the products of digestion are likely to be absorbed by the cytoplasm of the enterocyte). If part of the material remains undigested, then the autophagolysosome is transformed into an autophagic vacuole, which is directed to the plasmalemma of the apical region of the enterocyte and releases its contents outside.

In the animals of the first experimental group, erosion, ulcers, numerous small, and sometimes quite extensive hemorrhages were observed much more frequently than in the previous study period 14 days after the burn. In the population of the columnar enterocytes with the brush border increased the content of dystrophic altered cells,

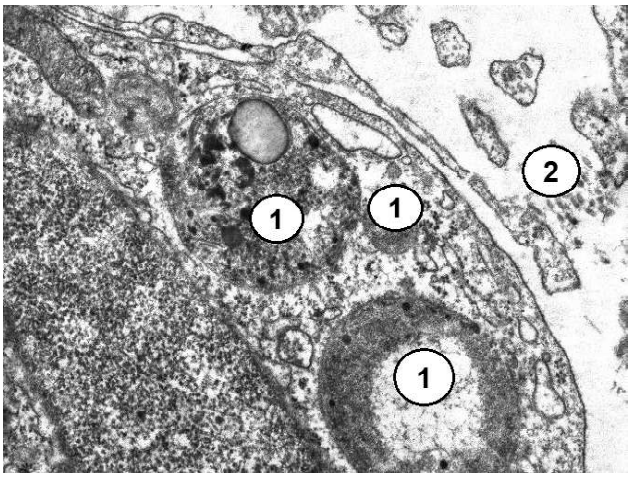

Fig. 5. Autophagosomes (1) of different size in the cytoplasm of enterocyte with a lost brush border in the mucous membrane of the duodenum of the rat of the first experimental group 14 days after burn, 2 - the remnants of the brush border. EM x20000.

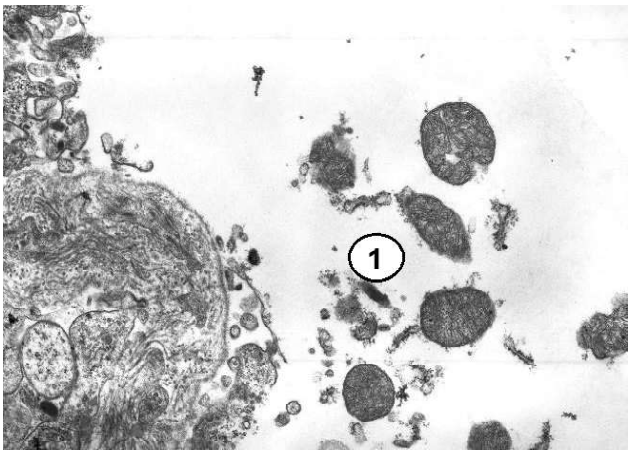

Fig. 6. Cellular detritus (1) in the intestinal lumen of the duodenum of the rat of the first experimental group 21 days after burn. EM x20000.

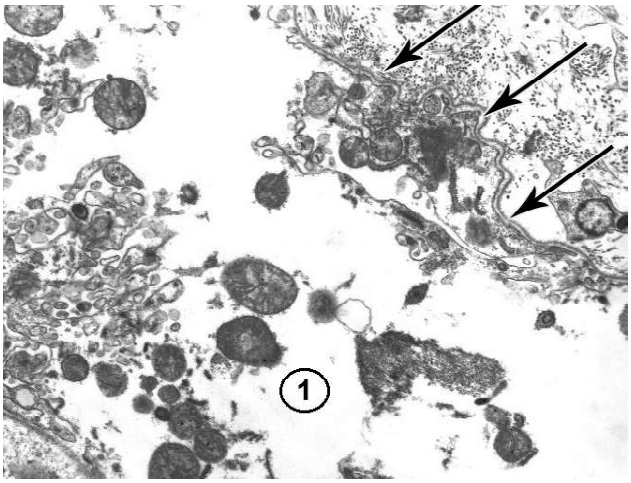

Fig. 7. Necrosis of the duodenal mucosa enterocytes of the rat of the second experimental group 14 days after burn. The arrows marked the "exposed" basement membrane of the epithelial monolayer. 1 - cellular detritus in the intestinal lumen. EM x20000.

which were located not only in the upper, but also the middle and lower part of the villi.

The sections of the epithelial monolayer of enterocytes with preserved brush border alternated with areas free of brush border. Enterocytes of the epithelial monolayer were adjacent to desquamated cells of varying degrees of conservation (Fig. 4). In the apical part of most enterocytes with partially lost brush border were located groups of rounded autophagosomes and autophagolysosomes of different size and content (Fig. 5).

In the cytoplasm of many enterocytes with the presence of structural site defects of the plasmalemma and nuclear membrane in conjunction with local damage of the cytoplasmic matrix (which, given their variability, can probably be repaired) revealed signs of increased functional activity of organelles (evidence of moderate expansion of the tubules of the granular endoplasmic reticulum, an increase in the number of ribosomes, the presence of polyribosome, the aggregation of intact mitochondria, the integrity of the nucleus). In other enterocytes, at this time, the cytoplasm is vacuolated in the form of various enlargement of the tubules of the endoplasmic reticulum with enlightenment of their contents, vacuolar transformation of mitochondria, which is completed by complete necrotic destruction and cell fragmentation with the formation of cellular detritus.

In animals of the first experimental group after 21 days, after burns, morphologically focal atrophy of the mucous membrane was manifested by thickening and shortening of the villi; in some places they were completely absent. The erosions that were the result of enterocyte necrosis were often found (Fig. 6).

In animals of the second experimental group, subtotal necrosis of enterocytes with a brush border is widespread 7 days after burn, when, while maintaining part of the cytoplasm with an intact border, the cell area is subjected to necrotic degeneration, and the formed cell detritus with microvilli of the border enters the intestinal space.

14 days after burn in the mucous membrane of the duodenum of animals of the second experimental group, enterocytes in certain areas of the epithelial monolayer are subject to complete necrotic decay. In these areas, the basement membrane becomes "exposed" (Fig. 7). It is quite well preserved and even, it is somewhat thick compared to that of the norm (in the control group of rats).

The structural changes described above are accompanied by deformation and destruction of the villi of the duodenal mucosa (Fig. 8). The villi lose their typical leaf-like shape, often take on a "twisted" shape, and filamentous villi appear, surrounded by groups of desquamated enterocytes and cellular detritus.

21 days after burns in animals of the second experimental group in some parts of the mucous membrane of the duodenum of the crypt and villi are clearly deformed. The villi lose their typical cytoarchitectonics and have the appearance of clustered (and sometimes

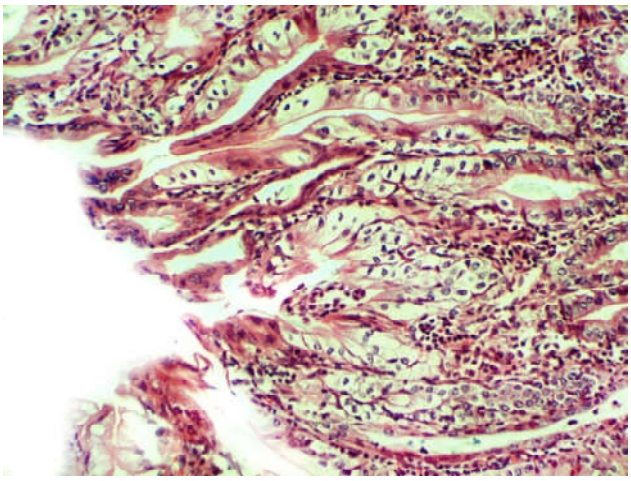

Fig. 8. Deformation and destruction of the villi of the duodenal mucosa of the second experimental group 14 days after burn. Hematoxylin-eosin. x60.

mushroom) enterocyte conglomerates of varying degrees of structural conservation.

Discussion

Diabetes mellitus and its related complications are becoming more common. The complex of gastrointestinal symptoms associated with diabetes is now known as diabetic enteropathy and can manifest as diarrhea, fecal incontinence, constipation, dyspepsia, nausea and vomiting [6]. The ancient theory that autonomic neuropathy is a major contributor to diabetic enteropathy has recently been supplemented by new theories of disease development. In particular, it is now considered [6] that hyperglycemia and its associated oxidative stress in neural networks (including nitric neurons and interstitial Cajal cells) play a central role in the development of diabetic enteropathy. The authors of the latest (at the time of publication) scientific review article "Diabets and the small intestine" [6] indicate that the latest scientific results are promising, but there is still a great need for further studies on the pathogenesis of diabetic enteropathy.

Many unresolved issues remain regarding the role of structural and functional alterations of the small intestine in the pathogenesis of burn disease, and, in particular, dysfunction in the context of burns of the intestinal epithelial barrier.

The data obtained indicate the structural manifestations of a barrier violation (destruction of dense interepithelial contacts, disappearance of interdigitations of cytoplasmic processes of adjacent enterocytes) in burn skin injury under experimental streptozotocin-induced diabetes. In addition, we confirmed the Huang Ya et al. data [11] regarding the involvement of autophagic processes in the development of gradual structural disorganization of the intestinal epithelial barrier, but unlike the authors, we consider their manifestation of an adaptive response.

It should be noted that the role of autophagy in cell death today by researchers treated quite contradictorily [11]. According to modern data [1], autophagy is the process of digestion of its own distorted organelles and sections of the cytoplasm by lysosomes (thus autophagy is both a type of programmed cell death and a strategy for cell survival by recycling cellular material). Thus, the adaptive response of the duodenal mucosa enterocytes to the destructive effects of burn disease factors involves the use as part of the plastic and energy resources of the degraded cellular material to repair the damaged enterocyte and to maintain its viability. Under the conditions of our experiment in rats of the first experimental group, the course of structural changes of enterocytes of the duodenal mucosa is slow enough to include the adaptive mechanism of autophagy of distorted organelles. In the animals of the second experimental group, destruction of cytoplasmic and organelle enterocyte sites (due to the summation of the factors of burn disease and diabetes) is accelerated and cells die by necrosis.

Summarizing we can say that in the duodenal mucosa of the second experimental group, the dynamics of morphological changes during different periods after burns (7 days - the stage of shock and early toxemia; 14 days - the stage of late toxemia; 21 days - the stage of septicemia) differ from animals of the first experimental group. Comparison of the obtained data with the previously revealed ones suggests that the time intervals and the nature of adaptive changes of the duodenal mucosa are largely prolonged and worsened. Significant lesions of the mucous membrane should lead to disruption of the processes of the digestive system, parietal digestion and absorption, as well as immunological protection (considering that the mucous membranes are the first zone of contact of the body with the antigens of the environment and the leading link of immune protection, immune defenses), affects the condition of the body of burned persons and, to a large extent, determines the development of burn disease, as well as the course of diabetes.

The prospect of further research in this area is related to the study of the effects on the duodenum of drugs that reduce the intoxication of the body and blood sugar level.

Conclusions

The results of the studies showed that the base of damage to the duodenal mucosa enterocytes consist of deep destructive changes, which after 21 days (in the stage of septicotoxemia), as a rule, are not reverse and develop on the background of significant intoxication of the body.

The structural changes of the enterocytes detected under the experiment were evidence of a violation of the structural integrity of the intestinal epithelial barrier. In animals of the first and (more) of the second experimental groups, the damaged epithelium of the duodenal mucosa critically weakens the adequacy of its function as an interface between the mucous membrane and the environment of the intestinal lumen, and is unable to structurally provide the reliability of antigenic toxicogenic bar.

In the mucous membrane of the duodenum in burn injury of the skin associated with diabetes is worsening of the manifestations of the adaptive reaction and prolongation of destructive processes, which is accompanied by a violation of intercellular interactions in the cytoarchitectonically altered and deformed crypts and villi.

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СТРУКТУРНІ ЗМІНИ ЕНТЕРОЦИТІВ СЛИЗОВОЇ ОБОЛОНКИ ДВАНАДЦЯТИПАЛОЇ КИШКИ ЩУРІВ ПРИ ОПІКОВІЙ ТРАВМІ ШКІРИ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО СТРЕПТОЗОТОЦИН-ІНДУКОВАНОГО ЦУКРОВОГО ДІАБЕТУ

Черкасов В.Г., Тімошенко І.О.

Робота присвячена вивченню структурних змін ентероцитів у слизовій оболонці дванадцятипалої кишки при опіковій травмі шкіри щура за умов експериментального стрептозотоцин-індукованого цукрового діабету. Дослідження проведено на лабораторних білих статевозрілих щурах-самцях масою 180-210 г. Контрольну групу склала 21 тварина без соматичної патології, першу експериментальну групу склали 21 щур з опіковою травмою шкіри, другу експериментальну групу склали 21 щур з опіком шкіри та експериментальним стрептозотоцин-індукованим діабетом. Модель експериментального цукрового діабету відтворювали шляхом введення щурам стрептозотоцину внутрішньоочеревинно одноразово в дозі 50 мг/кг. При експериментальному моделюванню опіку шкіри дві мідні пластинки у вигляді еліпсу витримували у воді при 100°С 10 хвилин і, за умов ефірного наркозу, накладали одночасно симетрично на обидві оголені частини тіла щурів з експозицією 10 секунд. Опікове пошкодження шкіри у щурів складало ІІА-Б ступеня - дермального поверхневого опіку (за старою класифікацією ІІІА ступінь) загальною площею 21-23% поверхні тіла з розвитком опікового шоку. Для морфологічних досліджень було вилучено відділ дванадцятипалої кишки, фрагменти якого були досліджені методами світлової та електронної мікроскопії. Основними критеріями оцінки пошкодження ентероцитів слизової оболонки дванадцятипалої кишки стали результати дослідження гістологічних та ультраструктурних даних в динаміці через 7, 14, та 21 добу після опіку шкіри. Результати проведених

досліджень показали, що в основі пошкоджень ентероцитів слизової оболонки дванадцятипалої кишки лежать глибокі деструктивні зміни, які через 21 добу (в стадії септикотоксемії), як правило, мають незворотній характер і розвиваються на фоні значної інтоксикації організму. При опіковій травмі шкіри, асоційованій з цукровим діабетом, в слизовій оболонці дванадцятипалої кишки погіршується прояв адаптивної реакції і пролонгуються деструктивні процеси, що супроводжується порушенням міжклітинних взаємодій в цитоархітектонічно змінених та деформованих ворсинках і криптах.
Ключові слова: *опікова травма, стрептозотоцин-індукований цукровий діабет, морфологічні зміни дванадцятипалої кишки.*

СТРУКТУРНЫЕ ИЗМЕНЕНИЯ ЭНТЕРОЦИТОВ СЛИЗИСТОЙ ОБОЛОЧКИ ДВЕНАДЦАТИПЕРСТНОЙ КИШКИ ПРИ ОЖОГОВОЙ ТРАВМЕ КОЖИ В УСЛОВИЯХ ЭКСПЕРИМЕНТАЛЬНОГО СТРЕПТОЗОТОЦИН-ИНДУЦИРОВАННОГО САХАРНОГО ДИАБЕТА

Черкасов В.Г., Тимошенко И.А.

Работа посвящена изучению структурных изменений энтероцитов в слизистой оболочке двенадцатиперстной кишки при ожоговой травме кожи крысы в условиях экспериментального стрептозотоцин-индуцированного сахарного диабета. Исследование проведено на лабораторных белых половозрелых крысах-самцах массой 180-210 г. Группу контроля составили 21 животное без соматической патологии, первую экспериментальную группу составила 21 крыса с ожоговой травмой кожи, вторую экспериментальную группу составила 21 крыса с ожогом кожи и экспериментальным стрептозотоцин-индуцированным диабетом. Модель экспериментального сахарного диабета воспроизводили путем введения крысам стрептозотоцина внутрибрюшинно однократно в дозе 50 мг/кг. При экспериментальном моделировании ожога кожи две медные пластинки в виде эллипса выдерживали в воде при 100°С 10 минут и, в условиях эфирного наркоза, накладывали одновременно симметрично на обе обнаженные части тела крыс с экспозицией 10 секунд. Ожоговое повреждение кожи у крыс составляло IIА-Б степени - дермального поверхностного ожога (по старой классификации IIIА степень) общей площадью 21-23% поверхности тела с развитием ожогового шока. Для морфологических исследований изымали отдел двенадцатиперстной кишки, фрагменты которого были исследованы общепринятыми методами световой и электронной микроскопии. Основными критериями оценки повреждения энтероцитов слизистой оболочки двенадцатиперстной кишки стали результаты исследования гистологических и ультраструктурных данных в динамике через 7, 14 и 21 сутки после ожога кожи. Результаты проведенных исследований показали, что в основе повреждений энтероцитов слизистой оболочки двенадцатиперстной кишки лежат глубокие деструктивные изменения, которые через 21 день (в стадии септикотоксимии), как правило, имеют необратимый характер и развиваются на фоне значительной интоксикации организма. При ожоговой травме кожи, ассоциированной с сахарным диабетом, в слизистой оболочке двенадцатиперстной кишки ухудшаются проявления адаптивной реакции и пролонгируются деструктивные процессы, сопровождающиеся нарушением межклеточных взаимодействий в цитоархитектонически измененных и деформированных ворсинках и криптах.
Ключевые слова: *ожоговая травма, стрептозотоцин-индуцированный сахарный диабет, морфологические изменения двенадцатиперстной кишки.*

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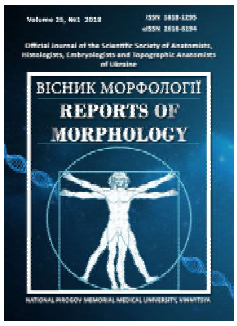

Indicators of the cell cycle in the thyroid gland in rats when applying infusion of 0.9% solution of NaCl, lactoprotein with sorbitol or HAES-LX 5%

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The thyroid gland is an important organ that is involved in the regulation of homeostasis and adaptation in various pathological conditions. However, the question of the study of the proliferative activity of thyroid cells by flow cytometry is still poorly understood. Purpose of study: to investigate the indices of the cell cycle and DNA fragmentation of thyroid cells in rats against the background of infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5%. Experimental studies were performed on 90 white male rats weighing 160-180 g. Infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5% was performed in the inferior vena cava after its catheterization in aseptic conditions through the femoral vein. The infusions were performed once a day for the first 7 days. Trunk catheterization and decapitation of animals (after 1, 3, 7, 14, 21, and 30 days) were performed under propofol anesthesia (60 mg/kg i/v). Within the framework of the agreement on scientific cooperation between the Research Center of National Pirogov Memorial Medical University, Vinnytsya and the Department of Histology, Cytology and Embryology of the Odessa National Medical University (from 01/01/2018), DNA content in the nuclei of thyroid cells of rats was determined by flow DNA cytometry. Cell cycle analysis was performed using the software FloMax (Partec, Germany) in full digital accordance with the mathematical model, which determined: G0G1 - the percentage of cells of the phase G0G1 to all cells of the cell cycle (DNA content = 2c); S - the percentage of the phase of DNA synthesis to all cells of the cell cycle (DNA content > 2c and < 4c); G2+M - the percentage ratio of the G2+M phase to all cells in the cell cycle (DNA = 4c). Determination of DNA fragmentation (SUB-G0G1, apoptosis) was performed by isolating the RN2 region on DNA histograms before the G0G1 peak, indicating nuclei of cells with a DNA content < 2c. The statistical processing of the obtained results was carried out in the license package "STATISTICA 6.1" using nonparametric estimation methods. The data obtained showed a virtually identical pattern of rat cell cycle and DNA fragmentation of the thyroid gland cells at all study times against the use of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5%. Thyroid cells in rats are predominantly in the inactive phase of DNA synthesis (G0G1) (90.32% - 91.88%), significantly fewer cells are in the G2+M phase (7.56% - 9.17%), and there is a small percentage of cells in the S-phase (DNA synthesis) (0.52% - 0.67%) and the SUB-G0G1 interval (DNA fragmentation, apoptosis) (2.23% - 2.81%). We can state that the activity of the main part of the thyroid gland is rather low without pathological irritation.

Keywords: *thyroid gland, DNA cytometry, cell cycle, 0.9% NaCl solution, lactoprotein with sorbitol, HAES-LX 5%.*

Introduction

The thyroid gland is an important organ that is involved in the regulation of homeostasis and adaptation in various pathological conditions [5, 13]. Numerous data on the morphological, biochemical and hormonal features of the thyroid gland in norm and pathology have been accumulated today [3]. However, the question of the

proliferative activity of organ cells remains poorly understood. Publications are devoted to the study of the proliferative activity of thyroid cells, mainly devoted to tumor and pre-tumor diseases [19, 20], which does not allow to extrapolate the obtained data to other pathological conditions.

It is known that the proliferative activity of the thyroid gland is a manifestation of physiological regeneration at the cellular level, with the number of cells in the state of mitotic division is normally in a small percentage [12]. Changes in the proliferative activity of cells in the thyroid gland depend on age, overall regeneration process and seasonal influences [11]. There is a significant increase in the proliferation of thyroid cells in pathology, which is associated with systemic activation of the body's neuroendocrine system by various factors [15]. It is known that the division of thyrocytes is controlled by central hormones, in particular thyroid tropic hormone and local modulators (growth factors, cytokines), which can stimulate both normal and pathological proliferation [17].

Changes in thyroglobulin in the colloid of the thyroid follicles are closely correlated with the phases of accumulation and evacuation of thyroid hormones having age, sex and circadian features. The relationships of proliferative activity, synthesis and resorption of thyroglobulin in thyroid cells are quite complex and mediated by a whole group of regulating factors of the gland itself and the hypothalamic-pituitary system [7].

A feature of cell proliferation in the thyroid gland, according to many researchers, is the process of desquamation of the follicular epithelium [9]. They argued that the basis of desquamation as a cellular destructive process may be a phenomenon such as apoptosis, and concluded that in the normal thyroid gland, the proliferation and desquamation of the follicular epithelium are antagonistic regulatory mechanisms that provide the necessary balance norms and pathologies.

Given the complexity of histological and morphological life-long study of the thyroid gland, there is a need to involve more accurate methods of studying cell division disorders. More than 60 imaging and evaluation markers have been proposed to determine apoptosis and cell proliferative activity. Proliferating cells that are at different stages of the mitotic cycle are immunohistochemically determined (Ki-67, PCNA, pl05, CDK-2, cdE) [8, 18]. In particular, these markers identify not only cells that have entered the mitosis, but also cells that are in the process of preparation for division, which allows to evaluate their proliferative potential [4]. However, the most informative method for assessing cell division is the flow cytometry method, which is nowadays defined as a reference for determining DNA fragmentation (apoptosis), and such that allows dividing the cell cycle into separate phases [1]. Flow cytometry method allowed estimation of changes in cell division and DNA fragmentation in various organs, in particular, endocrine ones, without pathological influence on the background of the use of infusion solutions [6, 10, 14].

Data on the study of indicators of the cell cycle of thyroid cells by flow DNA cytometry in non-tumor pathology, we have not revealed.

The *aim* of the study was to investigate the indices of the cell cycle and DNA fragmentation of thyroid cells in rats against the background of infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5%.

Materials and methods

Experimental studies were performed on 90 white male rats weighing 160-180 g (obtained from the vivarium of the Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine), conducted on the basis of the Research Laboratory of Functional Morphology and Genetics of the Research Center of National Pirogov Memorial Medical University, Vinnytsya. The keeping and manipulation of animals was carried out in accordance with the "General Ethical Principles of Animal Experiments", adopted by the First National Congress on Bioethics (Kyiv, 2001), also guided by the recommendations of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985), guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine on "Preclinical studies of medicinal products" (2001), as well as the rules of humane treatment for experimental animals and conditions approved the Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (Minutes No. 1 of 14.01.2010).

The infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5% was performed into the inferior vena cava after catheterization in aseptic conditions through the femoral vein. The catheter was sewn under the skin, its lumen filled along the entire length with a titrated heparin solution (0.1 ml heparin per 10 ml 0.9% NaCl solution) after each substance administration. The infusions were performed once a day for the first 7 days. Trunk catheterization and decapitation of animals (after 1, 3, 7, 14, 21, and 30 days) were performed under propofol anesthesia (60 mg/kg i/v).

Within the framework of the agreement on scientific cooperation between the Research Center of National Pirogov Memorial Medical University, Vinnytsya and the Department of Histology, Cytology and Embryology of the Odessa National Medical University (from 01.01.2018), DNA content in the nuclei of thyroid cells of rats was determined by flow DNA cytometry. Samples were prepared using a CyStain DNA Step 1 (Partec, Germany) nuclear DNA test solution according to the manufacturer's instructions. The use of this solution allows rapid extraction of nuclei and labeling nuclear DNA with 4`,6-diamidino-2-phenylindole (DAPI). CellTrics 50 μm disposable filters (Partec, Germany) were also used for sample production. Flow analysis was performed on a multifunctional flow cytometer "Partec PAS" (Partec, Germany), at the Research Center of

National Pirogov Memorial Medical University, Vinnytsya.

Ultraviolet radiation was used to excite DAPI fluorescence. 10 thousand events were subjected to each test sample. Cell cycle analysis was performed using the software FloMax (Partec, Germany) in full digital compliance according to a mathematical model, which determined:

G0G1 is the percentage of G0G1 phase cells to all cells in the cell cycle (DNA content = 2c);

S is the percentage of the phase of DNA synthesis to all cells of the cell cycle (DNA content >2c and <4c);

G2+M is the percentage ratio of the G2+M phase to all cells in the cell cycle (DNA = 4c).

Determination of DNA fragmentation (SUB-G0G1, apoptosis) was performed by isolating the RN2 regions on DNA histograms before the G0G1 peak, indicating nuclei of cells with a DNA content <2c.

The statistical processing of the obtained results was carried out in the license package "STATISTICA 6.1" using nonparametric estimation methods. The significance of the difference in values between the independent quantitative values was determined using the Mann-Whitney U test for the independent samples.

Results

The data obtained showed an identical pattern of cell cycle and DNA fragmentation of rat thyroid cells at all study times against the use of 0.9% NaCl solution, lactoprotein with sorbitol, or HAES-LX 5% in rats (Table 1). Among all cell cycle indices studied, only the S-phase indicator in the group with the introduction of 0.9% NaCl solution after 1 and 21 days had a slight trend of differences (p = 0.076).

The results of a study of DNA content in the cells of the thyroid gland of animals against the introduction of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5% showed the predominance of cells in the G0G1 phase (see Table 1). A much smaller number of cells were in a state of proliferation (S-phase, G2+M phase) (see Table 1). The level of cells with signs of apoptosis (SUB-G0G1) was negligible (see Table 1).

Figure 1 shows an example of a DNA histogram of thyroid cells after 3 days against the background of the introduction of 0.9% NaCl solution, in which the SUB-G0G1 interval was 2.44% of the total cellular events.

Figure 2 shows an example of a DNA histogram of thyroid cells after 7 days against the background of the introduction

Table 1. Indicators of the cell cycle in the thyroid gland of rats against the background of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5% according to flow cytometry DNA (M±σ).

Indicators of the cell cycle	Groups of animals			p	p_1	p_2
	0.9% NaCl (n=5)	LPS (n=5)	HAES-LX 5% (n=5)			
After 1 day from the beginning of the experiment						
G0G1	91.16±2.41	90.87±1.69	90.68±1.93	>0.05	>0.05	>0.05
S	0.652±0.134	0.548±0.118	0.638±0.162	>0.05	>0.05	>0.05
G2+M	8.192±2.368	8.576±1.759	8.682±1.855	>0.05	>0.05	>0.05
SUB-G0G1	2.462±0.800	2.814±0.707	2.688±0.870	>0.05	>0.05	>0.05
After 3 days from the beginning of the experiment						
G0G1	90.99±2.48	90.39±2.11	90.21±1.78	>0.05	>0.05	>0.05
S	0.622±0.110	0.600±0.047	0.616±0.134	>0.05	>0.05	>0.05
G2+M	8.392±2.375	9.008±2.129	9.174±1.811	>0.05	>0.05	>0.05
SUB-G0G1	2.594±0.628	2.410±0.825	2.480±0.812	>0.05	>0.05	>0.05
After 7 days from the beginning of the experiment						
G0G1	90.90±2.17	91.06±1.68	90.32±1.78	>0.05	>0.05	>0.05
S	0.650±0.139	0.672±0.133	0.592±0.076	>0.05	>0.05	>0.05
G2+M	8.448±2.113	8.276±1.647	9.084±1.757	>0.05	>0.05	>0.05
SUB-G0G1	2.632±0.724	2.510±1.006	2.662±0.711	>0.05	>0.05	>0.05
After 14 days from the beginning of the experiment						
G0G1	91.29±1.49	90.54±1.69	91.24±1.85	>0.05	>0.05	>0.05
S	0.562±0.153	0.658±0.168	0.586±0.146	>0.05	>0.05	>0.05
G2+M	8.146±1.520	8.798±1.736	8.176±1.881	>0.05	>0.05	>0.05
SUB-G0G1	2.304±0.835	2.812±0.772	2.326±1.096	>0.05	>0.05	>0.05
After 21 days from the beginning of the experiment						
G0G1	90.60±2.48	91.88±1.74	90.60±2.11	>0.05	>0.05	>0.05
S	0.522±0.075	0.556±0.166	0.594±0.157	>0.05	>0.05	>0.05
G2+M	8.986±2.370	7.558±1.595	8.804±2.187	>0.05	>0.05	>0.05
SUB-G0G1	2.622±0.677	2.742±0.513	2.266±0.623	>0.05	>0.05	>0.05
After 30 days from the beginning of the experiment						
G0G1	91.16±1.82	90.84±1.94	91.31±2.49	>0.05	>0.05	>0.05
S	0.592±0.193	0.590±0.216	0.582±0.133	>0.05	>0.05	>0.05
G2+M	8.252±1.851	8.570±1.767	8.110±2.409	>0.05	>0.05	>0.05
SUB-G0G1	2.630±0.717	2.600±1.013	2.232±0.417	>0.05	>0.05	>0.05

Notes: LPS - lactoprotein with sorbitol; p - indicator of significance differences between similar groups of 0.9% NaCl solution and lactoprotein with sorbitol; p_1 -index of significance differences between similar groups of 0.9% NaCl solution and HAES-LX 5%; p_2 - indicator of significance of differences between similar indicators of lactoprotein with sorbitol groups and HAES-LX 5%.

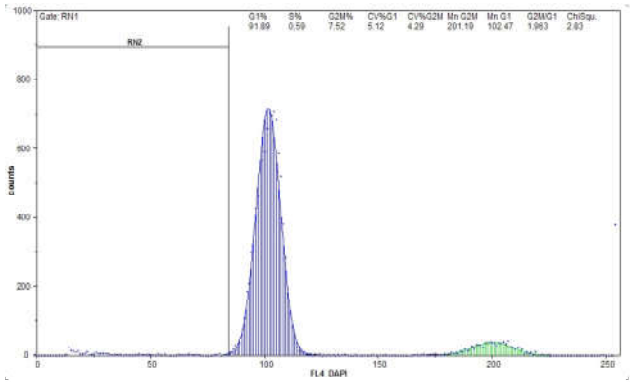

Fig. 1. DNA histogram of the nuclear suspension of thyroid cells after 3 days against the background of the introduction of 0.9% NaCl solution. RN2 (SUB-G0G1, DNA fragmentation) = 2.44%.

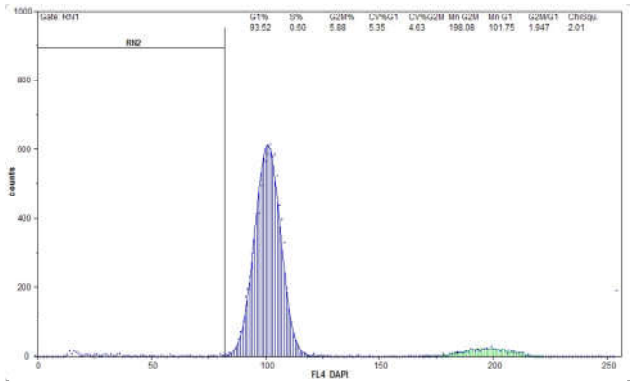

Fig. 2. DNA histogram of the nuclear suspension of thyroid cells after 7 days on the background of infusion with lactoprotein with sorbitol. RN2 (SUB-G0G1, DNA fragmentation) = 2.69%.

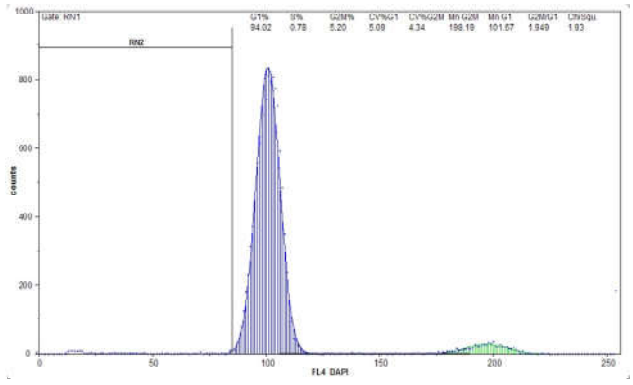

Fig. 3. DNA histogram of nuclear suspension of thyroid cells after 21 days without thermal skin burn on the background of infusion with HAES-LX 5%. RN2 (SUB-G0G1, DNA fragmentation) = 1.91%.

of lactoprotein with sorbitol, in which the interval SUB-G0G1 was 2.69% of the total number of cellular events.

Figure 3 shows an example of a DNA histogram of thyroid cells after 21 days on the background of the introduction of the first seven days of HAES-LX 5% solution, in which the SUB-G0G1 interval was 1.91% of the total cellular events.

According to our study, when using 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5%, it is established that the overwhelming percentage of cells is in the inactive phase G0G1 (range from 90.32±1.78% to 91.88±1.74%), significantly fewer number cells are in the G2+M phase (range from 7.558±1.595% to 9.174±1.811%), there is a small percentage of cells with signs of apoptosis (SUB-G0G1) (range from 2.232±0.417% to 2.814±0.707%) and in S-phase (DNA synthesis) (range from 0.522±0.075% to 0.672±0.133%).

Discussion

The study of thyroid cell cycle indices in rats by flow cytometry without pathological effects on the background of infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5% revealed that their use has no significant effect on the cell cycle fragmentation indices DNA of cells. Also, the determination of cell cycle indices and DNA fragmentation of thyroid cells against the background of infusion of 0.9% NaCl solution, lactoprotein with sorbitol or HAES-LX 5%, allowed to eliminate the potential impact on the normal cycle of gland cells, which was found in similar studies application of these solutions [6, 14]. It should be noted that the data obtained by us generally correspond to similar studies on the proliferative activity of thyroid cells in animals and humans [12, 21]. In studies of the processes of DNA synthesis and apoptosis in thyroid cells carried out by other methods [16], similar data were obtained regarding the relatively low level of synthesis and apoptosis of thyroid cells in animals without pathology.

It is also worth noting that other researchers [21] found a negative dependence of cell proliferation and increased induction of apoptosis in the thyroid gland as animals age increase, which is consistent with a general tendency to decrease the rate of cell renewal with age. There are also similar data regarding the age-related changes in the microstructure of the human thyroid gland [2]. We did not find signs of active apoptosis in this organ and little activity of DNA synthesis against the background of using the investigated solutions, which suggests that there is a balance between the processes of death and the renewal of the cell population of the thyroid gland. We can say that the activity of the main part of the cells is rather low without pathological irritation, which, in general, is in line with current views on the thyroid cell population and its functioning [13].

Our study has complemented the current understanding of the state of proliferative activity of thyroid cells under conditions of infusion solutions using flow cytometry. Given that we have not identified data on studies of the cell cycle and DNA fragmentation of thyroid cells and this technique is one of the benchmarks for the evaluation of apoptosis and cell division phases, we can state its priority in this area of research.

Conclusions

1. Infusion of 0.9% solution of NaCl, lactoprotein with sorbitol or HAES-LX 5% for duration of 7 days does not

affect the cell cycle and DNA fragmentation of the thyroid gland cells.

2. Thyroid gland cells in rats are predominantly in the inactive phase of DNA synthesis (G0G1) (90.32% - 91.88%), significantly fewer number of cells are in the G2+M phase (7.558% - 9.174%), there is a small percentage of cells in the S-phase (DNA synthesis) (0.522% - 0.672%) and the interval SUB-G0G1 (DNA fragmentation, apoptosis) (2.232% - 2.814%).

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ПОКАЗНИКИ КЛІТИННОГО ЦИКЛУ В ЩИТОПОДІБНІЙ ЗАЛОЗІ У ЩУРІВ ПРИ ЗАСТОСУВАННІ ІНФУЗІЇ 0,9% РОЗЧИНУ NACL, ЛАКТОПРОТЕЇНУ ІЗ СОРБІТОЛОМ АБО HAES-LX 5%

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Щитоподібна залоза є важливим органом, який бере участь у регуляції гомеостазу та адаптації при різних патологічних станах. Однак, питання вивчення проліферативної активності клітин щитоподібної залози методом проточної ДНК-цитометрії залишається маловивченим. Мета роботи: дослідити показники клітинного циклу та фрагментації ДНК клітин щитоподібної залози у щурів на фоні інфузії 0,9% розчину NaCl, лактопротеїну із сорбітолом або HAES-LX 5%. Експериментальні дослідження проведені на 90 білих щурах-самцях масою 160-180 г. Інфузію 0,9% розчину NaCl, лактопротеїну із сорбітолом або HAES-LX 5% проводили у нижню порожнисту вену після її катетеризації в асептичних умовах через стегнову вену. Інфузії виконували раз на добу на протязі перших 7 діб. Катетеризацію магістральних судин та декапітацію

тварин (через 1, 3, 7, 14, 21 та 30 діб) здійснювали в умовах пропофолового наркозу (60 мг/кг в/в). У рамках угоди про наукову співпрацю між науково-дослідним центром Вінницького національного медичного університету ім. М.І.Пирогова та кафедрою гістології, цитології та ембріології Одеського національного медичного університету (від 01.01.2018), вміст ДНК в ядрах клітин щитоподібної залози щурів визначали методом проточної ДНК-цитометрії. Аналіз клітинного циклу виконували засобами програмного забезпечення FloMax (Partec, Німеччина) у повній цифровій відповідності згідно математичної моделі, де визначали: G0G1 - відсоткове співвідношення клітин фази G0G1 до всіх клітин клітинного циклу (вміст ДНК = 2с); S - відсоткове співвідношення фази синтезу ДНК до всіх клітин клітинного циклу (вміст ДНК > 2с та < 4с); G2+M - відсоткове співвідношення фази G2+M до всіх клітин клітинного циклу (ДНК = 4с). Визначення фрагментації ДНК (SUB-G0G1, апоптоз) було виконано шляхом виділення ділянки RN2 на ДНК-гістограмах перед піком G0G1, яка вказує на ядра клітин з вмістом ДНК < 2с. Статистична обробка отриманих результатів була проведена в ліцензійному пакеті "STATISTICA 6.1" із застосуванням непараметричних методів оцінки. Отримані дані засвідчили практично ідентичну картину показників клітинного циклу та фрагментації ДНК клітин щитоподібної залози щурів в усі терміни дослідження на фоні використання 0,9% розчину NaCl, лактопротеїну з сорбітолом або HAES-LX 5%. Клітини щитоподібної залози в щурів переважно знаходяться в неактивній фазі синтезу ДНК (G0G1) (90,32% - 91,88%), значно менша кількість клітин перебувають в фазі G2+M (7,56% - 9,17%), наявний незначний відсоток клітин в S-фазі (синтез ДНК) (0,52% - 0,67%) та показника інтервалу SUB-G0G1 (фрагментація ДНК, апоптоз) (2,23% - 2,81%). Можемо стверджувати про досить невисоку активність основної частини клітин щитоподібної залози без патологічного подразнення.

Ключові слова: *щитоподібна залоза, ДНК-цитометрія, клітинний цикл, 0,9% розчин NaCl, лактопротеїн з сорбітолом, HAES-LX 5%.*

ПОКАЗАТЕЛИ КЛЕТОЧНОГО ЦИКЛА В ЩИТОВИДНОЙ ЖЕЛЕЗЕ У КРЫС ПРИ ПРИМЕНЕНИИ ИНФУЗИИ 0,9% РАСТВОРА NACL, ЛАКТОПРОТЕИНА С СОРБИТОЛОМ ИЛИ HAES-LX 5%

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Щитовидная железа является важным органом, который принимает участие в регуляции гомеостаза и адаптации при различных патологических состояниях. Однако, вопрос изучения пролиферативной активности клеток щитовидной железы методом проточной ДНК-цитометрии остается малоизученным. Цель работы: исследовать показатели клеточного цикла и фрагментации ДНК клеток щитовидной железы у крыс на фоне инфузии 0,9% раствора NaCl, лактопротеина с сорбитолом или HAES-LX 5%. Экспериментальные исследования проведены на 90 белых крысах-самцах массой 160-180 г. Инфузию 0,9% раствора NaCl, лактопротеина с сорбитолом или HAES-LX 5% проводили в нижнюю полую вену после ее катетеризации в асептических условиях через бедренную вену. Инфузии выполняли раз в сутки в течение первых 7 дней. Катетеризацию магистральных сосудов и декапитацию животных (через 1, 3, 7, 14, 21 и 30 суток) осуществляли в условиях пропофолового наркоза (60 мг/кг в/в). В рамках соглашения о научном сотрудничестве между научно-исследовательским центром Винницкого национального медицинского университета им. Н.И. Пирогова и кафедрой гистологии, цитологии и эмбриологии Одесского национального медицинского университета (от 01.01.2018), содержание ДНК в ядрах клеток щитовидной железы крыс определяли методом проточной ДНК-цитометрии. Анализ клеточного цикла выполняли средствами программного обеспечения FloMax (Partec, Германия) в полном цифровом соответствии согласно математической модели, где определялись: G0G1 - процентное соотношение клеток фазы G0G1 ко всем клеткам клеточного цикла (содержание ДНК = 2с); S - процентное соотношение фазы синтеза ДНК ко всем клеткам клеточного цикла (содержание ДНК>2с и <4с); G2+M - процентное соотношение фазы G2+M ко всем клеткам клеточного цикла (ДНК = 4с). Определение фрагментации ДНК (SUB-G0G1, апоптоз) было выполнено путем выделения участка RN2 на ДНК-гистограммах перед пиком G0G1, указывающая на ядра клеток с содержанием ДНК < 2с. Статистическая обработка полученных результатов была проведена в лицензионном пакете "STATISTICA 6.1" с применением непараметрических методов оценки. Полученные данные показали практически идентичную картину показателей клеточного цикла и фрагментации ДНК клеток щитовидной железы крыс во все сроки исследования на фоне использования 0,9% раствора NaCl, лактопротеина с сорбитолом или HAES-LX 5%. Клетки щитовидной железы у крыс преимущественно находятся в неактивную фазу синтеза ДНК (G0G1) (90,32% - 91,88%), значительно меньшее количество клеток находятся в фазе G2+M (7,56% - 9,17%), имеется незначительный процент клеток в S-фазе (синтез ДНК) (0,52% - 0,67%) и показателя интервала SUB-G0G1 (фрагментация ДНК, апоптоз) (2,23% - 2,81%). Можем утверждать о достаточно невысокой активности основной части клеток щитовидной железы без патологического раздражения.

Ключевые слова: *щитовидная железа, ДНК-цитометрия, клеточный цикл, 0,9% раствор NaCl, лактопротеин с сорбитолом, HAES-LX 5%.*

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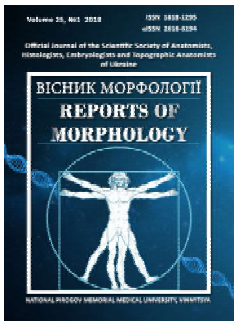

Mathematical modeling of individual parameters of the sum of the sizes intervertebral discs of the lumbar spine in juvenile males and males of the first mature age in norm

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In nowadays, an important area in medicine is the early preclinical identification of the parameters deviations from the norm, where mathematical modeling can help, which should be used to calculate individual linear parameters of internal structures based on external parameters of the body. The aim of the study was to calculate the individual total linear measures of the lumbar intervertebral discs in juniors and men of the first adulthood (17-28 years) in norm. The total size of the each intervertebral discs were calculated a sum of the anterior-posterior diameter, frontal diameter and vertical sizes of each lumbar intervertebral discs, which were measured by MRI. The next step was to calculate the relative proportional nonlinear somato-disc rates (based on body weight and body length) for each individual examined. Mathematical processing of the measured parameters and the relative values of the somato-disc relationships was carried out by the statistical data processing program "STATISTICA 6.1" using parametric methods. The correct distribution of the variational series indicators, mean values and their standard errors were evaluated. Based on relative values the mathematical model was created to obtain individual values of the total size of the lumbar intervertebral discs. Subsequently, we compared the measured total discs sizes of the anterior-posterior, frontal diameters and vertical sizes of the lumbar intervertebral discs with a mathematically calculated value for each lumbar intervertebral discs. The significant difference between the mathematically calculated and measured values of the total intervertebral discs' sizes of the didn't exceed 10%. Determination of the standard linear dimensions of the intervertebral discs of the lumbar spine using CT and MRI and comparison with theoretically calculated indices will make it possible to diagnose early manifestations of the lumbar intervertebral discs pathology.

Keywords: *modeling, intervertebral disc, lumbar spine, norm, juniors.*

Introduction

More than 200 million people are suffering from osteoporosis and musculoskeletal system diseases, according to WHO, occupy 4th place as a cause of disability and mortality in the world [13]. According to recent statistics from the International Osteoporosis Foundation, worldwide, 1 in 3 women over the age of 50 years and 1 in 5 men will experience osteoporotic fractures in their lifetime [25]. The experts predict an epidemic of osteoporosis, indicating the aging of the world population [5, 9]. Every fifth inhabitant of the globe suffers from back pain. In Ukraine chronic musculoskeletal system is also one of the most frequent problems [1, 15], and about 3.5 million people really familiar with the problems of the musculoskeletal system, it's terrible complications [11, 12], which require continuous long-term therapy [17, 18]. Degenerative disc diseases are an insidious illnesses that carefully hiding the other diseases symptoms, which significantly complicates their diagnosis, especially in the early stages.

The objective linear anterior-posterior diameter (APD), frontal diameter (FD) and vertical size (VS) of intervertebral discs, are not used in medical practice as criteria for evaluating their deviation from norm. Existing normative standards of intervertebral discs (IVD) linear sizes can be find in particular scientific works only and are not widely

used in medical practice. Thus, a method for evaluating the partial dimensions of the lumbar IVD [6] submits a calculation of the average values of the IVD sizes without taking into account their gender differences and individual anthropometric measures. Setting of relative measures - the only way to take into account the personal characteristics of each human body, which makes it possible to estimate norms or the early-onset pathological alterations [7, 23].

Mathematical models as relative indicators for modeling of the personal norm as a whole exist [8, 22, 26]. However, they ensure for the estimation of sagittal and transverse size only and don't include IVD height index, which is a key of pathological changes expression.

Meanwhile, the multiple supplementary anthropometric dimensions are difficulty identified and applied, that significantly restricts their widespread clinical use.

The purpose of the study: based on mathematical modeling to explore the individual parameters of the total size of the lumbar IVDs in juniors and men of the first adulthood (17-28 years) in norm.

Materials and methods

The 74 juniors and men of the first adulthood (17-28 years) without clinical manifestations of spine diseases were included in observation team. Individual comprehensive anthropometric investigation was performed for each research teams' persons and measured general (body length and body weight) and particular sizes (the longitudinal, the transverse and the circumference sizes, and skin-fat folds' thickness); lumbar spine MRI with the measuring of anterior-posterior diameter, frontal diameter and vertical size of the lumbar IVD was performed. Mathematical modelling by determining of the relative proportional nonlinear somato-disc value (based on body length and body mass) and calculating the total size of lumbar IVDs for every single person included in the study was undertaken. The TS of lumbar IVDs, which calculated as a sums of the anterior-posterior diameters, frontal diameters and vertical sizes of the lumbar IVDs and math modeling obtained dates were compared.

Mathematical processing of the measured parameters and the relative values of the somato-disc relationships was carried out by the statistical data processing program "STATISTICA 6.1" using parametric methods. The correct distribution of the variational series indicators, mean values and their standard errors were evaluated. The stepwise regression analysis method was used to create a mathematical model and predict the individual dimensions of the lumbar IVDs in practically healthy juniors and first adulthood males, depending on the body mass-growth parameters.

Results

The correlating of the external body measurements and the parameters of IVDs gives an affirmative answer to the question about their quantitative rates proportionality. Nevertheless, the correlations are too common and straight up, and unconnected with polymorphic structures. A clearer definition of multiple correlations (covariates) is a regression analysis that makes it impossible to determine the covariates of vertebral dimensional data with somatotypes. Regression analysis more strongly and accurate determines the proportional interrelations between body parameters and parameters of IVD.

Creation of the most optimal regression polynomial in predictability, a number of indicators, and the opportunity of logic verbal explanation is the major challenge of the investigation. The dependent variables are the lumbar IVDs measures (the IVDs total sizes as a sum of linear sizes of the APD, FD and VS of the lumbar IVDs). Graphical presentations depict interrelations between the IVDs total sizes of L_1-L_2 lumbar segments and the weight-length rates with a 95% confidence interval and show possibility to predict data of 72 from 74 cases in the given limits of reliability (Fig. 1).

The nature of the location is systemic and indicate the availability of patterns. Scattering diagram of the IVDs total sizes of the L_2-L_3, L_3-L_4, L_4-L_5 lumbar segments and relative magnitudes of the related mass-growth rate at a 95% confidence interval, they are possible to predict 72 cases out of 74 (Fig. 2).

Actually, the interrelation is at a higher level for relative terms - the relative magnitude of the weight-length rate and the IVD total size L_1-L2 segment (IVD1) from the weight-length rate (Fig. 3).

Graphical presentations depict interrelations between the IVDs total sizes of L_2-L_3, L_3-L_4, L_4-L_5 lumbar segments and the weight-length rates with a 95% confidence interval and show possibility to predict data of 73 from 74 cases in the given limits of reliability (Fig. 4).

The direct stepwise regression analysis requires particularly fulfilling several conditions. Firstly, is the value of the F-criterion, which must be at least 2.00, and the final regression polynoms result should have a coefficient of determination (R^2) at least 0.80, it means predictability more

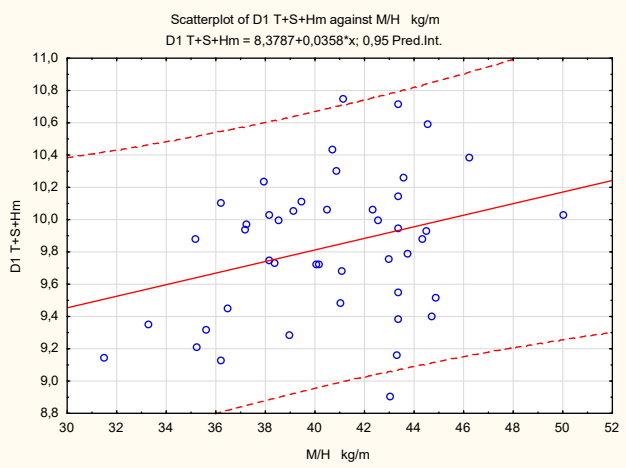


Fig. 1. Scattering diagram of IVD1 total size (L1-L2 segment) and weight-length rate.

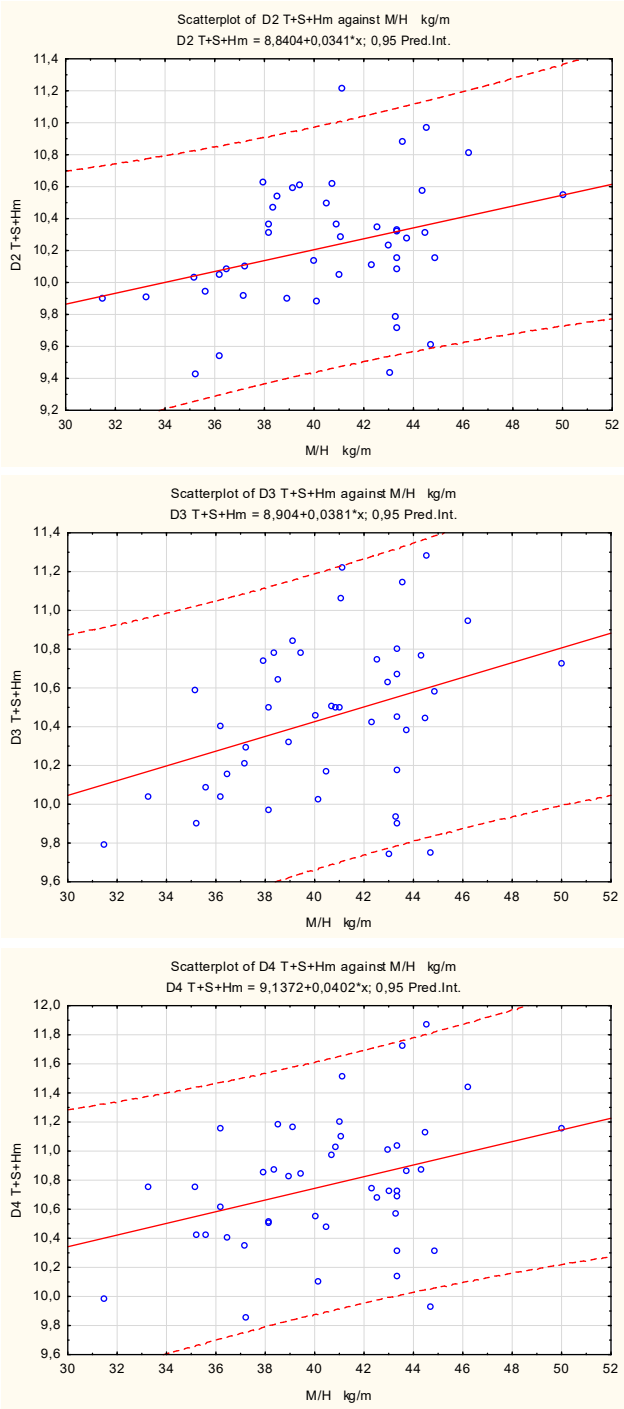


Fig. 2. Scattering diagrams of IVDs (IVD2, IVD3, IVD4) total size and weight-length rate.

than 80%.

This task requires to determining of the lumbar IVDs Total sizes of the L_1-L_5 segments in juniors and men of the first adulthood (17-28 years) in a norm based on the value of the weight-length rate and includes the preliminary regression modeling of the relative proportional coefficient of the weight-length rate per unit length of total sizes IVDs for the all lumbar IVDs of the L_1-L_5 segments. Determining the relative proportional nonlinear somato-disc values and the weight-length rates for each person in norm were carried out. The regression equations composition and characteristics for each listed lumbar IVD are summarized in Tables 1-4.

Coefficient of determination R^2, as a quality indicator of proximity (degree of predictability) is above 80.4%, which allows predicting dependent variable with the same rate. The standard error of the regression represents the average distance of observed values scattering fall from the regression line, in this case is a 0.165.

According to Table 1, the final regression model is as follows:

K/S_{D1} = (6,705+0,051*m-3,520*H) (predictability is 80.4%), where (here and thereafter): *SD_1 is the total size of IVD_1 in norm (MRI data) in cm; K - weight-length rate (in kg/m); m - body weight (in kg); H - body length (in meters).*

According to Table 2, the final regression model is as follows:

K/S_{D2} = (6,184+0,049*m-3,243*H) (predictability is 84,6%).

According to Table 3, the final regression model is as follows:

K/SD_3 = (6,592+0,048*m-3,475*H) (predictability is 87,3%).

According to Table 4, the final regression model is as follows:

K/SD_4 = (6,822+0,047*m-3,612*H) (predictability is 86.02%).

F-statistic is a global test to check for model with critical value 2.42 for number of variations, which in our case, F is from 91.27 - 152.35 (that is much more than the critical value, on the basis of which we can assert that the regression linear polynomial is significant ($p < 0.000001$). The deviations and predicted values graph demonstrates the almost linear dependence, so the suggestion of a normal distribution of errors is complete, that is, the model

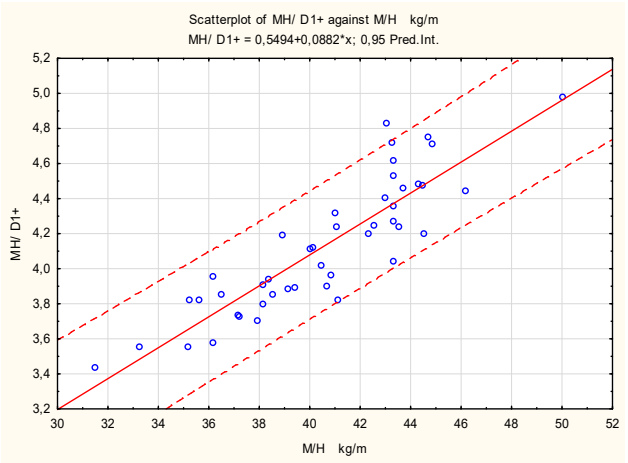


Fig. 3. Scattering diagram of the relative magnitude of the weight-length rate and the IVD1 total size from the weight-length rate.

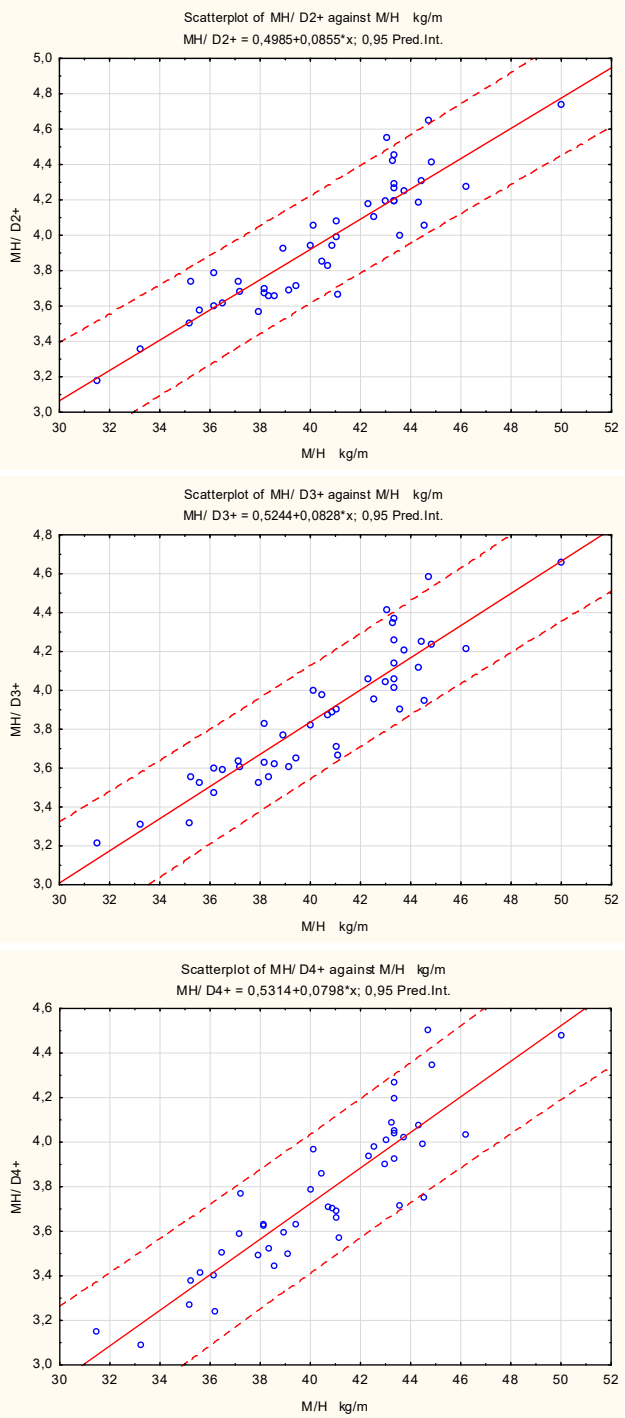


Fig. 4. Scattering diagram of the weight-length rates relative magnitudes and the IVD total size L2-L5 segments (D2, D3, D4) from the weight-length rate.

is an appropriate (Fig. 5, 6).

Check the adequacy of regression models was defined in the analysis of differences between the predictive and relative actual parameter values to each other. Obviously maximum relative deviations make up generally no more than 9%.

Table 1. The final results of direct stepwise regression analysis of the relative weight-length rate and the IVD total size L1-L2 segment using the body length and weight juniors and men of the first adulthood (17-28 years) in norm.

R=0.902 R^2=0.813 Adjusted **R^2=0.804** F(2,42)=91.27 p<0.0000 Standard error of estimation 0,165						
№=74	BETA	Standard error BETA	B	Standard error B	t(71)	p-value
Free index			**6.705**	0.831	8.064	0.0000
Body length (in m)	-0.513	0.075	**-3.520**	0.514	6.845	0.0000
Body weight (in kg)	1.011	0.075	**0.051**	0.003	13.49	0.0000

Table 2. The final results of direct stepwise regression analysis of the relative weight-length rate and the IVD total size L2-L3 segment using the body length and weight juniors and men of the first adulthood (17-28 years) in norm.

R=0.926 R^2=0.853 Adjusted **R^2=0.846** F(2.42)=121.9 p<0.0000 Standard error of estimation 0.138						
№=74	BETA	Standard error BETA	B	Standard error B	t(71)	p-value
Free index			**6.184**	0.693	8.926	0.0000
Body length (in m)	-0.503	0.066	**-3.243**	0.428	-7.570	0.0000
Body weight (in kg)	1.038	0.066	**0.049**	0.003	15.60	0.0000

Table 3. The final results of direct stepwise regression analysis of the relative weight-length rate and the IVD total size L3-L4 segment using the body length and weight juniors and men of the first adulthood (17-28 years) in norm.

R=0.937 R^2=0.879 Adjusted **R^2=0.873** F(2.42)=152.4 p<0.0000 Standard error of estimation 0.121						
№=74	BETA	Standard error BETA	B	Standard error B	t(71)	p-value
Free index			**6.592**	0.607	10.84	0.0000
Body length (in m)	-0.558	0.060	**-3.475**	0.376	-9.244	0.0000
Body weight (in kg)	1.049	0.060	**0.048**	0.003	17.39	0.0000

Table 4. The final results of direct stepwise regression analysis of the relative weight-length rate and the IVD total size L4-L5 segment using the body length and weight juniors and men of the first adulthood (17-28 years) in norm.

R=0.9319 R^2=0.867 Adjusted **R^2=0.860** F(2.42)=136.43 p<0.0000 Standard error of estimation 0.125						
№=74	BETA	Standard error BETA	B	Standard error B	t(71)	p-value
Free index			**6.822**	0.627	10.87	0,0000
Body length (in m)	-0.589	0.063	**-3.612**	0.388	-9.314	0.000
Body weight (in kg)	1.038	0.063	**0.047**	0.003	16.39	0.0000

As the second step of modeling, the further algebraic converting of the obtained proportions equation to determine the TS of three linear sizes for each lumbar IVDs in norm from the values of body weight and length.

Accordingly, after transferring the total sum of linear dimensions to the left-hand side of the equation, we obtained the following final results:

SD_1 = K/(6,705+0,051*m-3,520*H) ± 9%
SD_2 = K/(6,184+0,049*m-3,243*H) ± 9%
SD_3 = K/(6,592+0,048*m-3,475*H) ± 9%
SD_4 = K/(6,822+0,047*m-3,612*H) ± 9%,

where: SD_1 - the sum of linear sizes IVD1 in norm (MRI measurement) in cm;

SD_2 - sum of linear sizes of IVD1 2 in norm (MRI measurement) in cm;

SD_3 - sum of linear sizes of IVD1 3 in norm (MRI measurement) in cm;

SD_4 - sum of linear sizes of IVD1 4 in norm (MRI measurement) in cm;

K - weight-growth rate (in kg / m);

m - body weight (in kg);

H - body growth (in meters).

The modeling is carried out by determining the relative proportional somato-disc rates based on the weight-growth rate and the calculation of the TS of the three linear sizes of personal IVDs of the L_1-L_5 segments in norm for each specific individual.

The standard error for these models is ±5.0%. The established math models based on stepwise regression analysis and algebraic proportions transformation allow us to determine the sum of standard MRIs of the sizes IVD_1, IVD_2, IVD_3 and IVD_4 of L_1-L_5 segments in the norm on the basis of available in practical medicine anthropometric method - determination of mass and body length from further obtaining a relative weight-length rate.

Non-linearity dependence of the amount of the three standard sizes IVD_1, IVD_2, IVD_3 and IVD_4 in norm and the weight-length rate is presented in the graphs (Fig. 7, 8).

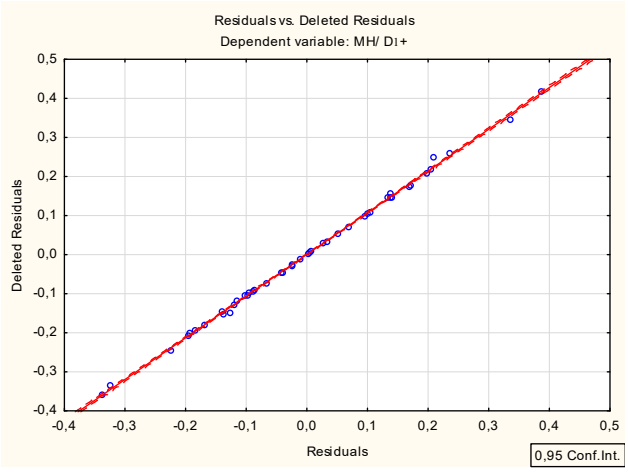
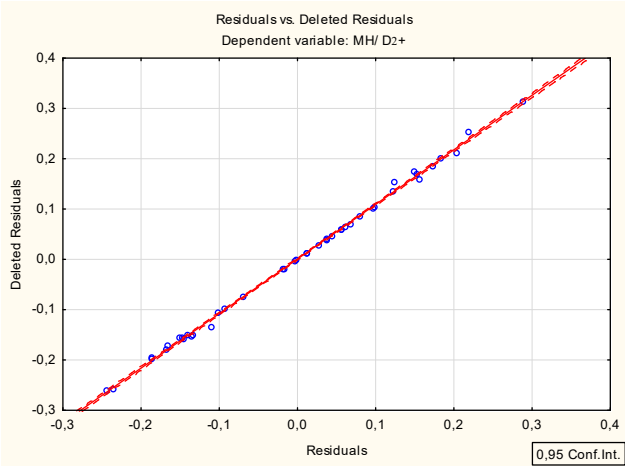
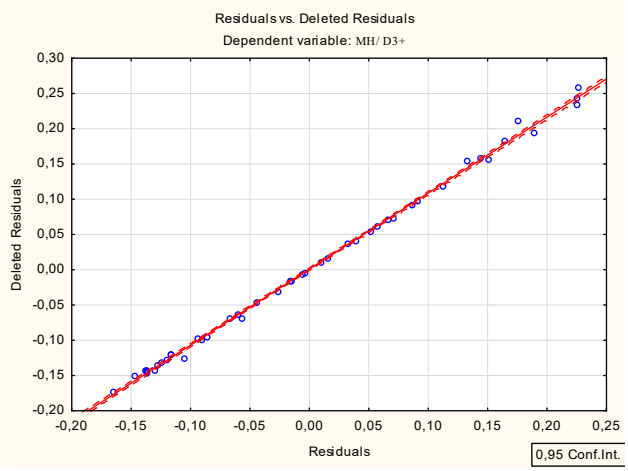


Fig 5. The scatter plot of the deviations and the predicted values of the total size lumbar IVD_1 in norm.





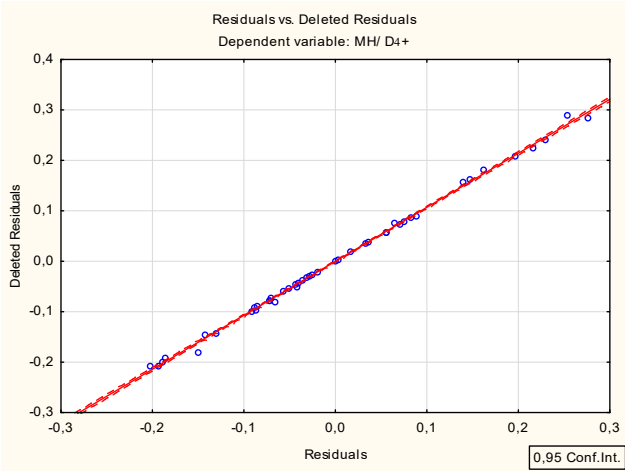


Fig. 6. The scatter plots of the deviations and the predicted values of the total sizes lumbar IVD_2, IVD_3 IVD_4 in norm.

Most predicted TS lumbar IVDs and the sum of measures obtained by MRI-morphometric examination does not significant difference and is within the 9% limit. The quantitative values of the deviations are presented in the diagram (Fig. 9).

The common trend of calculated personal measures is to reduce the range of linear studied parameters and

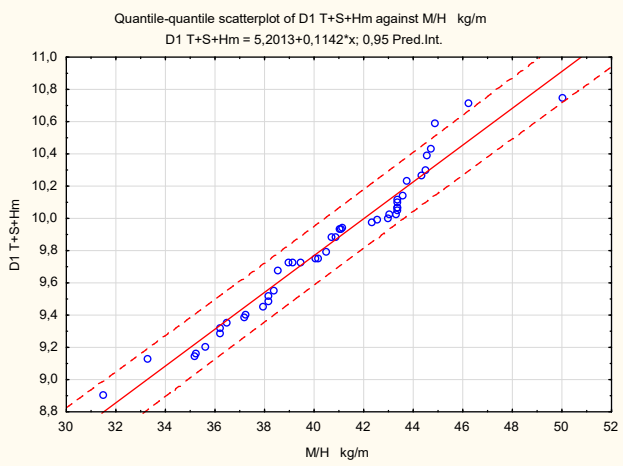
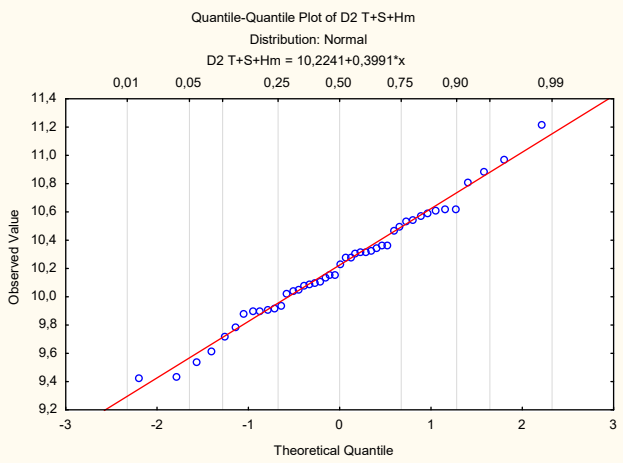


Fig. 7. Non-linear correlation of the TS of lumbar IVD1 and weight-length rate juniors and men of the first adulthood (17-28 years) in norm.

can reasonably be said, that individual normal ranges are within ±9% of the calculated ones.



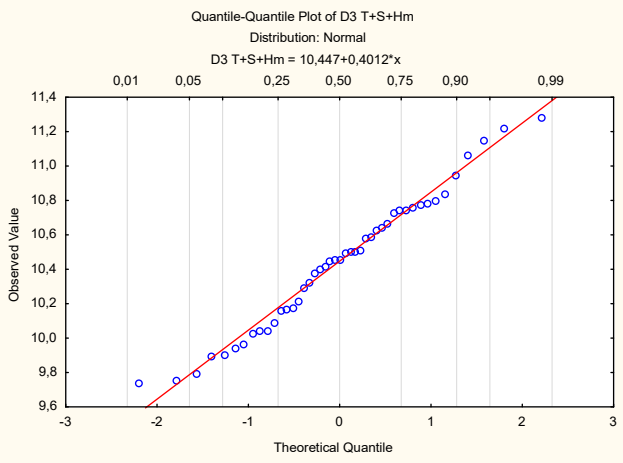
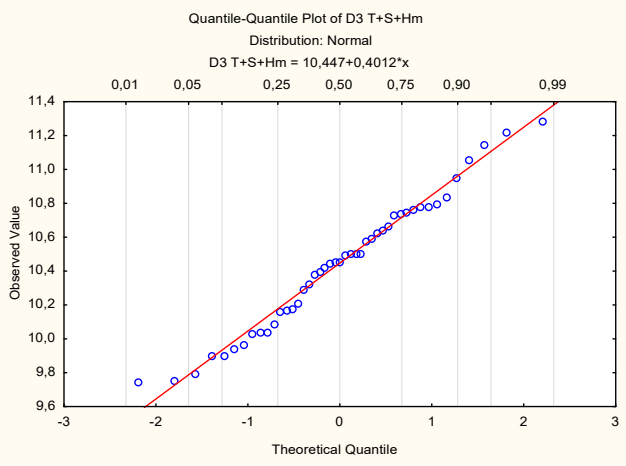


Fig. 8. Non-linear correlations of the TS lumbar IVD2, IVD3, IVD4 and weight-length rate juniors and men of the first adulthood (17-28 years) in norm.



Continue Fig. 8.

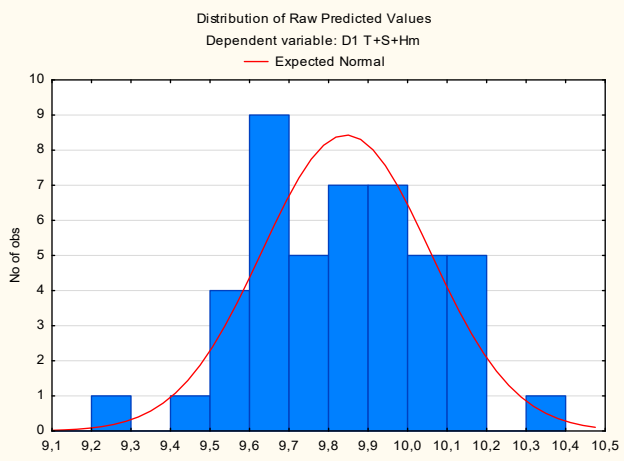


Fig. 9. Quantitative deviations values of real TS lumbar IVDs measured by MRI juniors and men of the first adulthood (17-28 years) in norm from the predicted values.

Discussion

The use of the proposed approach allows direct prognostic evaluation of the total value of standard linear MRI dimensions of the lumbar IVDs to diagnose early stages of intervertebral disc disease by MRI and CT scans.

There are examples in the scientific literature of the use of modeling to calculate the individual parameters of intervertebral discs and vertebral bodies [2, 3, 10, 19, 21, 26].

The interrelation of such individual factors as gender and age with linear dimensions of the spine and its' individual elements has been described, but few studies have considered the importance of other individual factors: body length, body weight and other anthropometric dates [16].

Some researchers noted the low correlation between anthropometric data and the cross-sectional area (CSA) of the vertebral endplates, and therefore expressed the inability to predict the area of the locking plates by anthropometric parameters; however, clear correlations were found in the size of the intervertebral discs and the

vertebral endplates [20].

D. Colombini et al. [4] found that the bone component of the body mass and wrist diameter had better correlation with the CSA of the lower lumbar intervertebral discs compared to the body weight index.

Z. Turk and D. Celan [27] proposed the mean square value of the width of the wrist, elbow and knee joint structures with the exception of the ankle diameter at the bone level to modeling the value of the CSA vertebrae endplates.

Degeneration of the intervertebral disc is a time-consuming process with a tendency to progress, so it is important to diagnose the earliest disc degeneration [24], including with early changes of the vertebrae endplates [14].

The automated systems programme development for determining of the linear organs' parameters, among them intervertebral discs, with minimal staff involvement in data processing, is a modern, promising method for automated evaluation of medical images [3, 28].

The analysis of the diagnostic value of the lumbar IVD total sizes modeling is showed high efficiency for detection of chondrosis and degenerative IVD changes.

The relevance and sensibility of the finding formulas in patients with various forms of acquired lumbar IVDs diseases which no abnormalities were detected in terms of linear parameters of intervertebral discs, calculated by existing methods. The assurance team was included juniors and men of the first mature age (17-28 years) with lumbar back pain, which had previously been diagnosed with chondrosis and disc degeneration. MRI of the lumbar spine were performed for respondents and measured the vertical, sagittal and transverse dimensions of the lumbar IVD between the bodies L_1-L_2, L_2-L_3, L_3-L_4, L_4-L_5. The personal parameters of the TS of the lumbar intervertebral discs for each respondent was modeled by the weight and growth data. Clinical testing of the model demonstrated significant difference TS IVDs in 46% of patients with a diagnosis of chondrosis and degenerative disc disease and the individually calculated TS IVDs. The obtained data represents the high sensitivity and informativity of the math modeling method.

Mathematical modeling, as a promising direction, can serve as a basis for calculating as for the individual standard linear sizes of the lumbar intervertebral discs, as the individual normal somato-organ parameters in the norm, which may serve as additional criteria for the detection of pathologies in the early stages, including automated diagnostic imaging systems.

Conclusions

1. Mathematical modeling can be basis for calculation of the individual normal parameters of the total size of the lumbar intervertebral discs (IVD) in juniors and men of the first mature age (17-28 years).

2. At the core of the model analysis lies the total size of the lumbar IVD three dimensions in a normal person, founded on the value of the weight-growth rate, which includes the of the previously created regression model of the relative proportional coefficient of the weight-growth rate per unit intervertebral discs' total sizes between 1 to 5 lumbar vertebrae. Modeling is performed by calculating of the relative proportional nonlinear somato-disc value founded on the weight-growth rate for each person in norm.

3. The investigation of standard linear measures of the lumbar IVD allows to diagnose the early stages diseases of the intervertebral discs by MRI and CT scans.

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МАТЕМАТИЧНЕ МОДЕЛЮВАННЯ ІНДИВІДУАЛЬНИХ ПАРАМЕТРІВ СУМИ РОЗМІРІВ МІЖХРЕБЦЕВИХ ДИСКІВ ПОПЕРЕКОВОГО ВІДДІЛУ ХРЕБТА В НОРМІ У ЮНАКІВ ТА ЧОЛОВІКІВ ПЕРШОГО ЗРІЛОГО ВІКУ

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В наш час важливим напрямком вдосконалення медицини є раннє доклінічне виявлення відхилень від норми, в чому може допомогти математичне моделювання, котре слід використовувати для розрахунку індивідуальних лінійних параметрів внутрішніх структур на основі зовнішніх параметрів тіла. Метою дослідження був розрахунок в нормі індивідуальних сумарних лінійних розмірів міжхребцевих дисків поперекового відділу хребта в юнаків та чоловіків першого зрілого віку (17-28 років). Сумарний розмір міжхребцевих дисків поперекового відділу хребта вираховували як суму виміряних міжхребцевих дисків поперекового відділу хребта: сагітального розміру, поперечного розміру та вертикального, котрі вимірювали на магнітно-резонансних томограмах. Наступним кроком було обчислення відносних пропорційних нелінійних сомато-дискових співвідношень (базуються на показниках маси та довжини тіла) для кожного із досліджених персонально. Математичну обробку виміряних параметрів та відносних величин сомато-дискових співвідношень проводили програмою статистичної обробки даних "STATISTICA 6.1" за допомогою параметричних методів. Оцінювали правильність розподілу показників варіаційного ряду, середні значення та їх стандартні помилки. На основі відносних показників була створена математична модель для отримання індивідуальних величин сумарного розміру міжхребцевих дисків поперекового відділу хребта. В подальшому провели порівняння виміряних сумарних показників сагітального, поперечного та вертикального розмірів міжхребцевих дисків з математично вирахуваною величиною для кожного міжхребцевого диску поперекового відділу хребта. Достовірна різниця математично передбачених та виміряних величин сумарних розмірів міжхребцевих дисків не перевищувала 10%. Визначення стандартних лінійних розмірів міжхребцевих дисків поперекового відділу хребта за допомогою КТ і МРТ та порівняння з теоретично розрахованими показниками дозволить діагностувати ранні прояви патології міжхребцевих дисків поперекового відділу хребтового стовбура.

Ключові слова: *моделювання, міжхребцевий диск, поперековий відділ хребта, норма, юнаки.*

МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ ИНДИВИДУАЛЬНЫХ ПАРАМЕТРОВ СУММЫ РАЗМЕРОВ МЕЖПОЗВОНКОВЫХ ДИСКОВ ПОЯСНИЧНОГО ОТДЕЛА ПОЗВОНОЧНИКА В НОРМЕ У ЮНОШЕЙ И МУЖЧИН ПЕРВОГО ЗРЕЛОГО ВОЗРАСТА

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В наше время важным направлением в медицине является раннее доклиническое выявление отклонений от нормы, в чем

может помочь математическое моделирование, которое следует использовать для расчета индивидуальных линейных параметров внутренних структур на основе внешних параметров тела. Целью исследования было рассчитать индивидуальные суммарные линейные размеры межпозвонковых дисков поясничного отдела позвоночника у юношей и мужчин первого зрелого возраста (17-28 лет) в норме. Суммарный размер межпозвонковых дисков поясничного отдела позвоночника вычисляли как сумму измеренных межпозвонковых дисков поясничного отдела позвоночника: сагиттального размера, поперечного размера и вертикального размеров, которые измеряли на магнитно-резонансных томограммах. Следующим шагом было вычисление относительных пропорциональных нелинейных сомато-дисковых соотношений (основываются на показателях массы и длины тела) для каждого исследуемого индивидуально. Математическую обработку измеренных параметров и относительных величин сомато-дисковых соотношений проводили программой статистической обработки данных "STATISTICA 6.1" с помощью параметрических методов. Оценивали правильность распределения показателей вариационного ряда, средние значения и их стандартные ошибки. На основе относительных показателей была создана математическая модель для получения индивидуальных величин суммарного размера межпозвонковых дисков поясничного отдела позвоночника. В дальнейшем провели сравнение измеренных суммарных показателей сагиттального, поперечного и вертикального размеров поясничных позвонков с математически рассчитанной величиной для каждого межпозвоночного диска поясничного отдела позвоночника. Достоверная разница математически рассчитанных и измеренных величин суммарных размеров межпозвонковых дисков не превышала 10%. Определение стандартных линейных размеров межпозвонковых дисков поясничного отдела позвоночника с помощью КТ и МРТ и сравнение с теоретически рассчитанными показателями позволит диагностировать ранние проявления патологии межпозвонковых дисков поясничного отдела позвоночного столба.

Ключевые слова: *моделирование, межпозвонквый диск, поясничный отдел позвоночника, норма, юноши.*

REQUIREMENTS FOR ARTICLES

For publication, scientific articles are accepted only in English only with translation on Ukrainian or Russian, which contain the following necessary elements: UDC code; title of the article (in English, Ukrainian and Russian); surname, name and patronymic of the authors (in English, Ukrainian and Russian); the official name of the organization (institution) (in English, Ukrainian and Russian); city, country (in English, Ukrainian and Russian); structured annotations (in English, Ukrainian and Russian); keywords (in English, Ukrainian and Russian); introduction; purpose; materials and methods of research; research results; discussion; conclusions; bibliographic references.

The title of the article briefly reflects its contents and contains no more than 15 words.

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The introduction reflects the state of research and the relevance of the problem according to the world scientific literature (at least 15 references to English articles in international journals over the past 5 years). At the end of the entry, the purpose of the article is formulated (contains no more than 2-3 sentences, in which the problem or hypothesis is addressed, which is solved by the author).

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The section should allow other researchers to perform similar studies and check the results obtained by the author. If necessary, this section may be divided into subdivisions. Depending on the research objects, the ethical principles of the European Convention for the protection of vertebrate animals must be observed; Helsinki Declaration; informed consent of the surveyed, etc. (for more details, see "Public Ethics and its Conflict"). At the end of this section, a "statistical processing of results" section is required, which specifies the program and methods for processing the results obtained by the automobile.

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In the discussion, it is necessary to summarize and analyze the results, as possible, compare them with the data of other researchers. It is necessary to highlight the novelty and possible theoretical or practical significance of the results of the research. You should not repeat the information already listed in the "Introduction" section. At the end of the discussion, a separate paragraph should reflect the prospects for using the results obtained by the author.

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