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CONTENT

DETERMINATION OF INFLUENCE OF AUXILIARY INGREDIENTS ON ANTIOXIDANT ACTIVITY OF EXTRACT OF LEAVES OF THE QUINCE AND GRAPES SEED MEAL IN PHYTOGEL WITH THE USE OF SPECTROMETRIC METHOD WITH THE DPPH INDICATOR SYSTEM

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Abstract

To study an impact of auxiliary substances on gel containing extracts of quince leaves and grape seed meal, which is based on polymethylsiloxane.

Pharmaco-technological and physicochemical methods. In this study, a spectrophotometric method is applied to determine an antioxidant activity of the gel.

We examined an impact of auxiliary substances on the gel. According to the results of studies we chose auxiliary ingredients which improve not only gustatory quality but also technological parameters. Applying spectrometric analysis, we investigated an antioxidant activity of phytogel. The gel has a structure of rigid matrix, which is built through a process of condensation of methylsilanetriol and siloxane bonds between the silicon atoms, which makes it possible to maintain and stabilize active natural ingredients. The experiment proved that the extract of leaves of quince and grape seed meal have some antioxidant activity. But, upon the introduction of stevia extract as a coregent taste, the gel that contains quince leaf extract and grape seed meal increases the antioxidant activity. Phytogel has antioxidant activity of 84 % relative to the reference sample, which suggests that the gel can resist the harmful effects of free radicals, which are constantly produced in the human organism.

It was confirmed that the addition of auxiliary substances into the gel with the extracts of quince leaves and grape seed meal based on polymethylsiloxane increases bioavailability and therapeutic efficiency, in particular, the antioxidant activity, of the gel.

Stevia extract as an adjuvant in the phytogel, as gustatory corrector, increases the antioxidant activity of phyto pharmaceutical drugs.

Keywords: antioxidant activity, phytogel, extracts of quince, grape, stevia, ascorbic acid.

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1. Introduction

The question about a formation of the antioxidant index and its use as an objective measure of positive effectiveness of antioxidant substances on human health as well as the indicator of high quality of functional pharmaceutical drugs is widely discussed in many countries [1–3].

Therefore analysis of antioxidant properties of natural substances and products, which are based on natural substances, is one of the important concerns nowadays.

Medicinal products with antioxidant properties are used for prevention of diseases caused by excessive quantity of free radicals, formed in human body under the influence of negative external factors [4, 5].

The need to update the assortment of domestic phytopreparations including an antioxidant effects is beyond doubt [6]. The modern aspect is a relatively assortment of natural raw materials, caused by high pharmacological activity and expressed clinical effects, among which significant place is occupied by the extract of quince leaf and grape seed meal [7, 8]. As it is known, the main pharmacological effect of the extract of red grapes (leaves, seeds, combs, and bagasse) is the strengthening vascular walls of veins and capillaries (P-vitamin activity). [9]. At present polyphenol complex is contained in the extract of grape seed meal that also has important therapeutic value and a high antioxidant activity [10].

Beyond doubt is the need to use the natural gastroprotective antiulcer medications in the treatment of peptic ulcer disease. This group of drugs directly protects the mucous the stomach from the irritating effects of external factors through the formation of ulcers on the surface of the protective cladding, which promotes scarring and prevents them from exposure to of gastric juice [11].

These substances include antioxidants natural. They regulate the normal activities of the human organism, in particular of oxidation lipid, protein and nucleic acid, resulting in cells which are formed highly active of oxygen compounds called free radicals. They, undoubtedly, show a therapeutic effect, and or other compounds that are contained in natural plants [12].

For example, quince leaves extract inhibits the proliferation of intestinal tumor cells and of renal adenocarcinoma cells [13]. Presence of chlorogenic acid in the extract, together with other antimicrobial determines polyphenolic compounds and antiviral activity. [14] Reported antiulcer activity of extracts of quince fruits on the model of ethanol-induced gastric ulcers [15].

The choice of inactive ingredients is a highly important step in the development of new pharmaceutical medicaments, as they can affect not only on the physical and chemical characteristics of pharmaceutical forms in the process of their production and storage, but also on therapeutic efficiency of the pharmaceutical drug itself [16].

We have selected and studied composition of the gel and proved its biological efficiency in our previous works.

The gel preparation technology is based on stage addition of active pharmaceutical ingredients and inactive ingredients [17, 18].

Flavors are important among inactive ingredients because unpleasant taste of pharmaceutical drugs can prevent to take this medicine.

Natural extract of stevia was chosen as a corrective agent.

It was done because of the following reasons: the regular use of stevia extract normalizes carbohydrate and fat metabolism in human body; cell regeneration and blood coagulation are being improved; and the growth of tumors slows down. The sweet secret stevia stevioside, contained in the molecule, which is a glycoside consisting of glucose, sucrose, and steviol of stevia extract is a complex stevioside. Numerous experiments have shown that regular use of an extract from stevia – reduced sugar levels in the blood, cholesterol and radionuclides in the body, improving cell regeneration and blood coagulation, inhibited the growth of tumors [19].

2. Aim of research

To determine an influence of auxiliary ingredients on bioavailability and therapeutic effectiveness, especially on antioxidant activity of gel with extract of quince leaves and grape seed meal, which is based on polymethylsiloxane.

3. Materials and methods

Researches were conducted when testing samples of the gels, made with similar pharmaceutical structure by means of similar technology [17].

At first polymethilsiloxane was dispersed to homogeneity in a separate container at a defined temperature and speed of the rotor mixer.

Measured amount of water, xanthan gum and sorbic acid were injected separately into heated flask.

Flask was heated to a temperature of 60 °C and mixture of above mentioned ingredients were blended until smooth.

Then the water phase was added to disperse polymethilsiloxane.

The mixture was stirred to obtain phytogel [17].

Further, all extracts were injected to this basis one after another, then they were stirred and afterwards some samples were taken.

Experimental procedure

Testing samples were held at room temperature for 8–12 hours and on their basis we prepared testing samples of – 10 % aqueous solution, which concentration amounts 30 mg/100 ml on a dry basis.

Our experimental studies of antioxidant activity were conducted by a modified method [20].

The principle of the method is based on the reduction of stable radical 2 2-diphenyl-1-picrylhydrazyl (DPPH) by antioxidant molecule. The result of this method is to change the optical density of the solution at 515 nm [21, 22].

Antioxidant activity (AOA) is expressed as % inhibition of DPPH radical, which is represented by the formula:

$$\% \text{ of inhibition} = [(A_0 - A_k)/A_0] * 100,$$

where A_0 – optical density at T=0 min (solution DPPH); A_k – optical density at T=10 min in the presence of antioxidant.

Measurements were performed on spectrophotometer Hewlett Packard 8452A with layer thickness of 10 mm cuvettes.

Ascorbic acid, in particular water solution of 30 mg/100, was chosen as a reference standard (reference sample), ml.

4. Results of research

Apparently from the chart, addition of gel with extract of leaves of a quince extract of meal of dark grades of grapes increases its antioxidant activity almost in 3 times, and addition of extract of leaves of a stevia leads to increase in antioxidant activity too. The results of research of samples of gel depending on its structure are presented on the chart (**Fig. 1**).

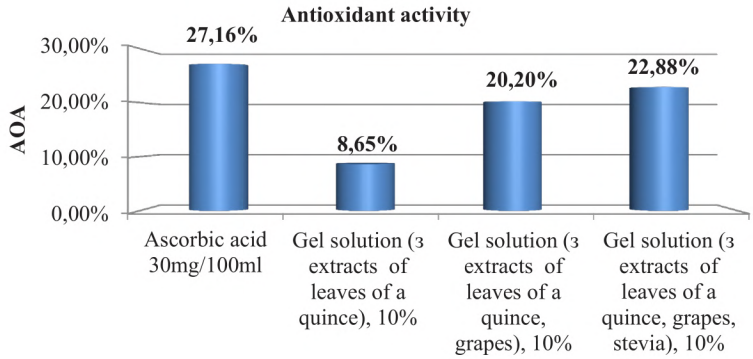

Fig. 1. Antioxidant activity of the gel depending on its composition

Recovery of the free radical DPPH of the gel with participation phenolic compounds from the extracts of leaves and quince seed meal grape kinetically passes slower than in the other two cases (**Table 1**). This confirms the feasibility of using the gel extract meal of dark grapes and extract of stevia leaves in the composition.

Results of the examination of gel samples, depending on their composition, are represented in the following table (**Table 1**).

Table 1
Antioxidant activity indicators

Product name	A_0	A_k	% AOA	% AOA relative to control
Ascorbic acid	0,83	0,6046	27,16	100
Gel with quince leaves extract)	0,8096	0,7396	8,65	31,84
Gel with quince leaves and grape extract	0,8149	0,6503	20,20	74,38
Gel with quince leaves, grape and stevia extract	0,8152	0,6287	22,88	84,24

According to results, which are shown in the table, addition of grape seed meal together with addition of stevia extract to an extract of quince leaves tripled the antioxidants activity of the gel.

The results of reduction of free radical DPPH in dynamic are presented graphically in **Fig. 2.**

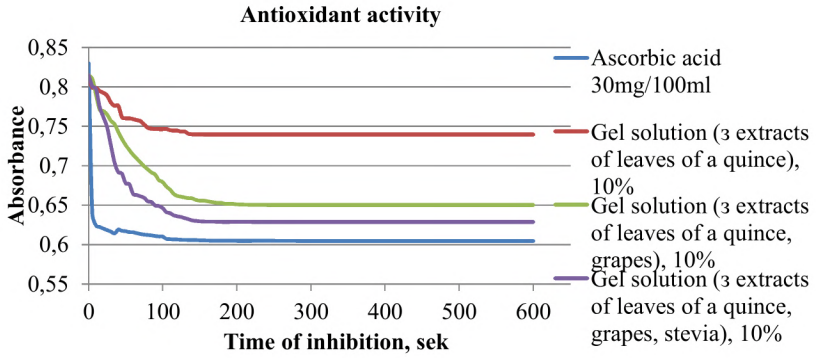

Fig. 2. Comparative antioxidant activity in the dynamic of the DPPH reduction

According to results which are shown in the **Fig. 2**, each of active ingredients shows antioxidant activity, in a varying degree, but in a complex, these components show higher antioxidant activity in comparison with reference sample.

Thus, the developed composition of gel with extracts of leaves of a quince and meal of grapes on the basis of polymethylsiloxane with excipients, shows the expressed antioxidant activity which on the recovery properties practically does not concede 0,03 % of solution of ascorbic acid.

5. Discussion

The study has shown that auxiliary ingredients, namely stevia extract, affect the bioactivity of the gel with extract of quince leaves and grape seed extract, which is based on polymethylsiloxane.

According to the results of the studies was selected technology for producing a gel with extracts of leaves quince and grape seed meal, based on polymethylsiloxane. With spectrometric analysis, we investigated Phytogel on antioxidant activity. The gel has a structure forming a rigid matrix, built through a process of condensation metilsilantriola and siloxane bonds between the silicon atoms, which makes it possible to maintain and stabilize the active natural ingredients. Experiment is proved that of the extract of quince leaves and grape seed meal, have certain antioxidant activity. But at technological introduction stevia extract as auxiliary ingredient is combined with other extracts of the gel to improve the gustatory characteristics, increasing the value of antioxidant activity. Phytogel has antioxidant activity 84 % on reference sample what can confront the damaging effect of free radicals, which are continuously produced in human organism.

6. Conclusions

1. It is established the influence of auxiliary ingredients, namely an extract of stevia, the bioavailability of the gel from the extracts of quince leaf and grape meal based on polymethylsiloxane. It is proved that the antioxidant activity is increased, with the introduction of coregent taste − stevia extract.

2. The spectrometer method with the indicator DPPH system was applied to definition of antioxidant activity of gel from extracts of quince leaves and of meal grapes on the basis of polimethylsiloxane, that gave the chance truly to estimate the select composition of gel at which it is possible to assume that preparations, except antiulcer activity, will show complex therapeutic action on a human organism due to high antioxidant activity.

References

[1] Shanin, Yu. N., Shanin, V. Yu., Zinov'ev, E. V. (2003). Antioksidantnaya terapiya v klinicheskoy praktike. Saint Petersburg: ELBY, 128.

[2] Mullen, W., Marks, S. C., Crozier, A. (2007). Evaluation of Phenolic Compounds in Commercial Fruit Juices and Fruit Drinks. Journal of Agricultural and Food Chemistry, 55 (8), 3148–3157. doi: 10.1021/jf062970x

[3] Korovina, N. A., Zakharova, I. N., Skorobogatova, E. V. (2007). Antioksidanty pri obostrenii khronicheskikh gastroduodenitov u detey. Vrach, 9, 79–81.

[4] Khadzhieva, Z. D., Kuznetsov, A. V., Biryukova, D. V. (2012). Tekhnologicheskie aspekti ispol'zovaniya vspomogatel'nykh veshchestv v proizvodstve lekarstvennykh preparatov. Fundamental research, 5, 436–440.

[5] Konkina, I. G., Grabovskij, S. A., Murinov, Yu. I., Kabal'nova, N. N. (2011). Sravnitelnaya otsenka reaktsionnoy sposobnosti kvertsetina i digidrokvertsetina po otnosheniyu k peroksilnyim radikalam. Himiya rastitel'nogo syirya, 3, 207–208.

[6] Spravochnyk lekarstvenykh sredstv, vypusk vos'moy (Hosudarstvennyy ekspertny tsentr MZ Ukrayny) (2015). Available at: http://mozdocs.kiev.ua

[7] Kurkin, V. A., Poroykov, V. V., Kurkina, A. V., Avdeeva, E. V., Pravdivtseva, O. E. (2015). Flavanoidy i lekarstvennyih rasteniy. Prognoz antioksidantnoy aktivnosti. Sovremennyie problem i nauki i obrazovaniya, 2. Available at: https://www.science-education.ru/ru/article/view?id=23252

[8] Kondratev, D. V., Scheglov, N. G. (2009). Sposobyi polucheniya ekstrakta vinogradnyih vyizhimok i vozmozhnosti ego ispolzovaniya v pischevoy promyishlennosti. Izvestiya vysshih uchebnyh zavedenij. Pishchevaya tekhnologiya. 1, 62–65.

[9] Dixon, R. A., Pasinetti, G. M. (2010). Flavonoids and Isoflavonoids: From Plant Biology to Agriculture and Neuroscience. Plant Physiology, 154 (2), 453–457. doi: 10.1104/pp.110.161430

[10] Yashin, Ya. I., Ryizhnev, V. Yu., Yashin, A. Ya., Chernousova, N. I. (2008). Prirodnyie antioksidantyi – nadezhnaya zaschita cheloveka ot opasnyih bolezney i stareniya. Moscow: NPO «Himavtomatika», 122.

[11] Dronova, M. A., Kiseleva, T. L., Smirnova, Yu. A. (2010). Sovremennyie preparatyi rastitelnogo proishozhdeniya dlya regulyatsii motornoy funktsii zheludochno-kishechnogo trakta. II Rossijskij fitoterapevticheskij s"ezd. Moscow, 32–35.

[12] Lutskiy, M. A., Kuksova, T. V., Smelyanets, M. A., Lushnikova, Yu. P. (2014). Svobodnoradikal'noe okislenie lipidov i belkov – universalnyiy protsess zhiznedeyatelnosti organizma. Uspehi sovremennogo estestvoznaniya, 12-1, 24–28.

[13] Carvalho, M., Silva, B. M., Silva, R., Valentao, P., Andrade, P. B., Bastos, M. L. (2010). First Report on Cydonia oblonga Miller Anticancer Potential: Differential Antiproliferative Effect against Human Kidney and Colon Cancer Cells. Journal of Agricultural and Food Chemistry, 58 (6), 3366–3370. doi: 10.1021/jf903836k

[14] Fattouch, S., Caboni, P., Coroneo, V., Tuberoso, C. I. G., Angioni, A., Dessi, S. (2007). Antimicrobial Activity of Tunisian Quince (Cydonia oblongaMiller) Pulp and Peel Polyphenolic Extracts. Journal of Agricultural and Food Chemistry, 55 (3), 963–969. doi: 10.1021/jf062614e

[15] Hamauzu, Y., Inno, T., Kume, C., Irie, M., Hiramatsu, K. (2006). Antioxidant and Antiulcerative Properties of Phenolics from Chinese Quince, Quince, and Apple Fruits. Journal of Agricultural and Food Chemistry, 54 (3), 765–772. doi: 10.1021/jf052236y

[16] Tarahovskiy, Yu. S., Kim, Yu. A., Abdrasilov, B. S., Muzafarov, E. N. (2013). Flavonoidyi: biohimiya, biofizika, meditsina. Puschino: Synchrobook, 310.

[17] Kuznyetsova, O. V., Buts'ka, V. Ye., Dzhan, T. V., Tymchenko, O. H. (2015). Obgruntuvannya rozrobky skladu ta doslidzhennya fizykokhimichnykh vlastyvostey helyu z ekstraktiv lystya ayvy y shrotu vynohradu na osnovi polimetylsyloksanu. Farmatsevtychnyy zhurnal, 4, 30–36.

[18] Kuznetsova, O. V., Lavrenchuk, G. Y., Buts'ka, V. E., Simonova, I. V. (2015). Farmakobiologichni vlastivosti ekstraktu shrotu temnikh sortiv vinogradu Farmakologiya ta likarska toksikologiya, 3, 70–75.

[19] Lyakhovkin, A. G., Nikolaev, A. P., Uchitel', V. B. (1999). Steviya – medovaya trava, rastenie lekarstvennoe i pishchevoe v vashem dome. Saint Petersburg, 96.

[20] Paulova, H., Bochorakova, H., Taborska, E. (2004). Metody stanoveni antioxidacni aktivity prirodnych latek in vitro. In Chemicke listy, 98 (4), 147–179.

[21] Vlasova, I. V., Vershinin, V. I., Tsyupko, T. G. (2011). Metodologiya spektrofotometricheskogo analiza smesey organicheskih soedineniy. Problema neadditivnosti svetopogloscheniya. Journal of Analytical Chemistry, 66 (1), 25–33.

[22] Yashin, Ya. I., Yashin, A. Ya. (2009). Problema opredeleniya soderzhaniya antioksidantov. Metrologiya, 8, 50–53.

THE LYMPH NODES IN RATS WITH EXPERIMENTAL TYPE 1 DIABETES MELLITUS (DM-1)

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Abstract

The aim is to study morphofunctional structure of NALT (nasal associated lymphoid tissue) and visceral lymph nodes of rats with experimental type 1 diabetes mellitus (DM-1) and to define the effectiveness of the treatment with herbal drug "Imupret".

Materials and methods: The experiment involved 20 animals, divided into 4 groups: the 1st group was the control group of healthy rats, the 2nd group was the control group subject to prophylactic treatment with "Imupret, the 3rd group included rats with experimental diabetes, and the 4th group included rats with experimental diabetes subject to treatment with "Imupret. Functional changes in immune organs were evaluated by the results of morphometric analysis; morphological pattern was evaluated by histo-structural changes.

Results. The research revealed that under conditions of diabetes mellitus type 1, the volume, area and density of the lymphoid tissue decreased, and only its "fine" cell was detected. The paper demonstrates the development of relative immune deficiency in immunocompetent organs in rats with diabetes mellitus type 1. The use of drug "Imupret" demonstrated its immunomodulatory function, which is especially important in terms of immunosuppression in patient with DM-1.

Conclusion. The received results are of a great clinical significance, and show the necessity of early prevention and treatment of immunity disorders under conditions of diabetes mellitus type 1.

Keywords: diabetes mellitus type 1, visceral lymph nodes, NALT, immunity histostructural changes, morphometric analysis.

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1. Introduction

In recent years, within increase of prevalence of immunodeficiency states of different genesis, doctors' interest in the immune system functioning increased significantly [1]. The immune system is known to have a close connection with the endocrine system, and is particularly affected under condition of such disease as diabetes mellitus type 1 (DM-1) [2]. Increased susceptibility to infections in patients with DM-1 is associated with impaired protective functions of the body as a result of suppressed immunity, enhanced cell adhesion of microorganisms, a tendency to catabolic processes. In the pathogenesis of DM-1 and many of its complications, an important place belongs to the violation of the functional capacity of the immune system, which is the subject of numerous studies [3]. In patients with diabetes mellitus, significant changes appears in chemotaxis, a decrease in the bactericidal activity of neutrophils, increased production of reactive oxygen species, leukotrienes, secretion of lysosomal enzymes, and changes in the level of intracellular calcium are often observed [4].

Morphological basis of the immune system is a lymphoid tissue, which is represented by the central and peripheral organs [5]. The structures protecting the mucous membrane are called mucosa associated lymphoid tissue – MALT. MALT consists of visceral lymph nodes of gastrointestinal tract, being the place to induce humoral (antibody mediated) and cellular immunity [6]. The analogue of such tissue in the conducting airway is the nasal-associated lymphoid tissue (NALT) or lymphoid tissue associated with the nasal cavity, which is the regional representative of submucosal of the immune system. It is localized as adjacent to the nasal mucosa and mucosa of the soft palate. NALT is inherent both to humans and rats, but the rats do not have tonsils; thus NALT for rats can be considered as the first immune

barrier to fight against external antigens in the digestive and respiratory systems [7]. In contrast to the well-characterized Peyer's patches, which are already present in fetal life and seem to be a constitutive part of the integrated mucosal immune system, the tissue genesis of NALT is different [8]. So far no data on NALT formation during embryogenesis in humans are available, but in rats and mice NALT has been observed only postnatal [9]. In fetal human larynges there is only a scattered distribution of immunocompetentcells, but no organized larynx-associated lymphoid tissue (LALT) [10]. Bronchus-associated lymphoid tissue (BALT) is sometimes present in the fetus, but associated mainly with infections, and develops after birth [11]. In the non-infected fetus BALT is found only rarely and in low density [12]. Therefore, the formation of respiratory MALT seems to be a reactive phenomenon in response to microbial stimulation. Dysregulation of mucosal immune responses might be a critical factor in the still unknown etiology of sudden infant death syndrome (SIDS) [13]. No data are available so far on the occurrence of NALT in human adults, as NALT is difficult to investigate in this age group because calcification inhibits adequate sampling and processing of tissue blocks [14]. MALT is characterised by the predominance of local dimeric IgA production, secreted as secretory IgA (sIgA) that is responsible for the immune exclusion of bacteria and viruses [15]. The term common mucosal immune system (CMIS) implies that activated lymphocytes derived from one mucosal surface can recirculate and localise selectively in other mucosal surfaces [16]. This connection between different mucosal surfaces permits immunity initiated at one anatomical site to protect other mucosal sites [17]. In rats, NALT is present at birth, earlier than BALT and this is probably due to its strategic position with respect to the incoming air [18]. As rats are obligate nasal breathers, the inspired air, laden with environmental antigens, passes the nasal cavities before it reaches the lungs. [19]. The particular interest from the point of view of clinical effectiveness has the combined herbal preparation BNO 1030 (Imupret) [20].

2. Aim of research

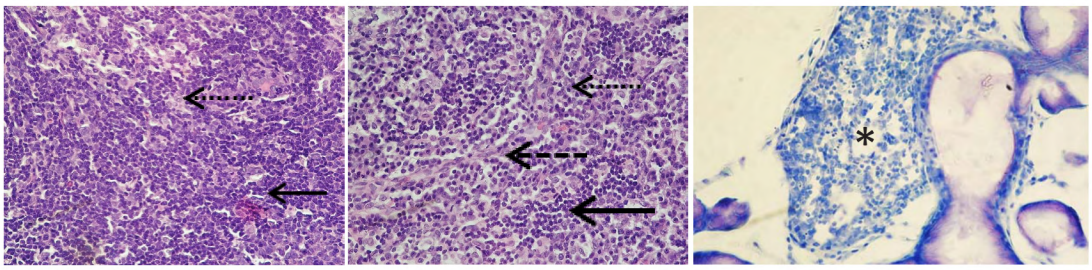
To study morphofunctional structure of NALT (nasal associated lymphoid tissue) and visceral lymph nodes of rats with experimental type 1 diabetes mellitus (DM-1) and to define the effectiveness of the treatment with herbal drug "Imupret".

3. Material and methods

The research involved intact Wistar male rats (20 animals in total), weighing 130−150 grams, under the conditions of experimental diabetes mellitus type 1. Experimental DM-1 for rats was induced by a single intraperitoneal introduction of Streptozotocin (S0130, Sigma-Aldrich Co. LLC, the USA), dose of 55.0 mg/kg, diluted in 0.1 M citrate buffer, pH 4.5. Rats of the same age in the control group got intraperitoneally 0.5 ml of 0.1 M citrate buffer, pH 4.5. After four weeks of diabetes development, within 14 days, rats got drug Imupret per os 0.05 ml/animal three times a day; chosen concentration meets guidelines for use of the daily dose for children over 12 years and adults, taking into account the factors of species stability for human and rats (0.45 and 1.89 respectively). Functional changes in immune organs were evaluated by the results of morphometric analysis. Qualitative histostructural changes were detected (such as appearance of germinal centers in lymphoid tissue nodules, changes in the density of lymphoid tissue); quantitative parameters were subject to statistical evaluation. Micro photographs were obtained using microscope Olympus BX 51. Morphometric analysis was performed with Carl Zeiss software (AxioVision SE64 Rel. 4.9.1), magnification ×400. All rats were divided in 4 groups, 5 animals in each one: the 1st group was the control group of healthy rats, the 2nd group was the control group subject to prophylactic treatment with "Imupret", the 3rd group included rats with experimental diabetes, and the 4th group included rats with experimental diabetes subject to treatment with "Imupret".

4. Results

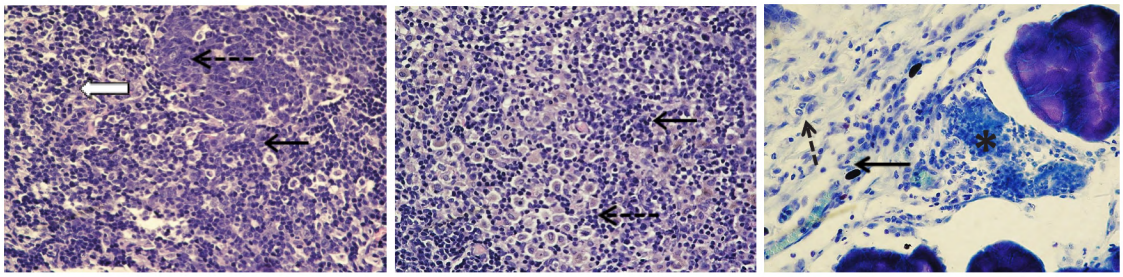
Visceral nodes in the control group of intact rats showed the normal morphological picture. NALT is small and has no signs of immune activation (**Fig. 1, *a*−*c***). In cortical substance (**Fig. 1, *a***) were registered lymphoid follicles, and moderate density lymphocytes were recorded in reticuloendothelial cells. In medulla (**Fig. 1, *b***) was registred a small number of lymphocytes and stromal elements of reticuloendothelial cells.



a *b* *c*

Fig. 1. Lymph node of control group: *a* – cortical substance; *b* – medulla.
Note: ⟵ – lymphocytes; ⇜····· – macrophages; ⇜--- – reticuloendothelial cells.
Hematoxylin-eosin; *c* – Nasal-associated lymphoid tissue (NALT).
* – Clusters of lymphocytes NALT. Toluidine blue

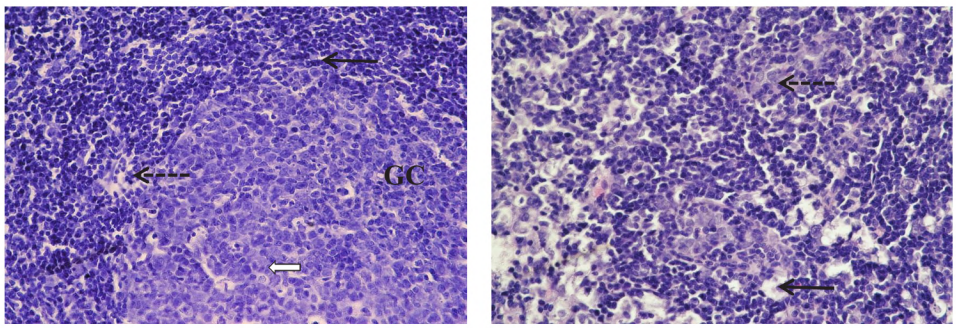
In rats with DM-1 we found the sings of reactive immune activation. In cortex of visceral nodes were registered lymphoid follicles, moderate density lymphocyte, activation of reticuloendotheliocytus, in medulla we found a small number of lymphocytes and stromal elements of reticuloendotheliocytus. In NALT it has been shown significant number of neutrophils and isolated basophils. (**Fig. 2, *a–c***).



a *b* *c*

Fig. 2. Lymph node of diabetic rats. *a* – cortical substance, *b* – medulla.
Note: ⟵ – lymphocytes; GC – germinal center (lymphoid reaction); ⇦ – cell in mitosis;
⇜--- – r eticuloendothelial cells. Hematoxylin-eosin; *c* – Nasal-associated lymphoid tissue (NALT).
Note: ⟵ – tissue basophils; ⇜--- – neutrophils; * – Clusters of lymphocyte NALT. Toluidine blue.

In diabetic rats, which were treated with Imupret, were found the signs of immune response. It was registered the increased density of lymphocytes, activation of mitosis and germinal center (**Fig. 3, *a, b***).



a *b*

Fig. 3. Lymph node of diabetic rats, which received Imupret. *a* – cortical substance; *b* – medulla.
Note: ⟵ – lymphocytes; GC – germinal center (lymphoid reaction);
⇦ – cell in mitosis; ⇜--- – reticuloendothelial cells

5. Discussion

Within the study of visceral nodes the control group of intact rats showed no inflammatory changes, signs of antigen presentation. The stromal elements of medulla, brain cords, and capsules showed no signs of reorganization. Only a few macrophages were recorded within the field of view. The volume of NALT was insignificant; in addition, there were recorded the tissue basophils without the signs of degranulation (**Fig. 1, *a*–*c***).

Within the study of visceral lymph nodes, the group with diabetes showed reactive changes of lymph node stroma; at morphological level it was manifested in the increasing number of epithelioreticular cells, increase of volume indicators (size of the nuclei and soma). Sinuses of the node showed an increase in the lymphoid cells density, from a moderate increase in the lymphocytes number (especially in individual sinuses) up to occurrence of the secondary nodes with clear germinal centers, being a manifestation of migration of B-lymphocytes and AG-presentation. The cells in mitosis were detected, which could indicate both the migration of immunocompetent cells, and their proliferation. Medullary substance also showed an increase in the lymphoid cells density as well as epithelioreticular cells and occurrence of groups of macrophages. These changes can be assessed as a manifestation of activation of the immune response, and as for the stromal elements, reorganization of the stroma in response to a volume increase of lymphoid tissue representation **Fig. 2, *a, b***.

The study of NALT in diabetic group of rats detected only its small focus with accumulation of groups of neutrophils and isolated basophils (**Fig. 2, *c***).

The group of rats with diabetes mellitus, treated with herbal drug "Imupret", showed in the visceral lymph nodes the appearance of significant germinal centers in the cortex of the lymph nodes, significant increase in the lymphocytes density, as well as isolated cells in mitosis. Medullary substance showed the cords of lymphoid cells, increase of lymphocytes density in the dural and portal sinuses (**Fig. 3, *a, b***).

The results of the research found out that morphological and functional state of lymphoid tissue is closely related to glucose metabolism. It revealed the signs of immunodeficiency among affected rats, both in visceral lymph nodes, and in NALT ($p<0,05$). In this group, morphometric analysis showed the increased number of epithelioreticular cells, increase of volume indicators (size of the nuclei and soma). Despite a wide range of antidiabetic drugs used in the clinic of DM-1 and its complications, now more attention is paid to the use of phytotherapy. One of the widely used phytopreparations at present is the Imupret, the mechanism of its action is not completely clarified.

In diabetic group of rats, which received Imupret, we demonstrated increased lymphocytes density in visceral lymph nodes and NALT ($p<0,05$).

6. Conclusions

1. The studied structures, i. e., visceral lymph nodes and NALT refer to the peripheral lymphoid organs; they have a similar structure, shown within the study of their histology.

2. The research demonstrated the changes in these organs in rats with DM-1, induced with Streptozotocin. It revealed the signs of immunodeficiency among affected rats, both in visceral lymph nodes, and in NALT.

3. Use of drug "Imupret" demonstrated its immunomodulatory function ($p<0,05$), which is especially important in terms of immunosuppression in patient with DM-1.

References

[1] Daneman, D. (2006). Type 1 diabetes. The Lancet, 367 (9513), 847–858. doi: 10.1016/s0140-6736(06)68341-4

[2] Muller, L. M. A. J., Gorter, K. J., Hak, E., Goudzwaard, W. L., Schellevis, F. G., Hoepelman, A. I. M., Rutten, G. E. H. M. (2005). Increased Risk of Common Infections in Patients with Type 1 and Type 2 Diabetes Mellitus. Clinical Infectious Diseases, 41 (3), 281–288. doi: 10.1086/431587

[3] Yang, H., Jin, X., Kei Lam, C. W., Yan, S.-K. (2011). Oxidative stress and diabetes mellitus. Clinical Chemistry and Laboratory Medicine, 49 (11), 1773–1782. doi: 10.1515/cclm.2011.250

[4] Knip, M., Veijola, R., Virtanen, S. M., Hyoty, H., Vaarala, O., Akerblom, H. K. (2005). Environmental Triggers and Determinants of Type 1 Diabetes. Diabetes, 54, S125–S136. doi: 10.2337/diabetes.54.suppl_2.s125

[5] Valle, A., Giamporcaro, G. M., Scavini, M., Stabilini, A., Grogan, P., Bianconi, E. et. al. (2013). Reduction of Circulating Neutrophils Precedes and Accompanies Type 1 Diabetes. Diabetes, 62 (6), 2072–2077. doi: 10.2337/db12-1345

[6] James, S., Perry, L., Gallagher, R., Lowe, J., Dunbabin, J., McElduff, P. et. al. (2014). Service usage and vascular complications in young adults with type 1 diabetes. BMC Endocrine Disorders, 14 (1). doi: 10.1186/1472-6823-14-39

[7] Szablewski, L., Sulima, A. (2016). The structural and functional changes of blood cells and molecular components in diabetes mellitus. Biological Chemistry, 398 (4), 411–423. doi: 10.1515/hsz-2016-0196

[8] Guzman-Bautista, E. R., Ramirez-Estudillo, M. C., Rojas-Gomez, O. I., Vega-Lopez, M. A. (2015). Tracheal and bronchial polymeric immunoglobulin secretory immune system (PISIS) development in a porcine model. Developmental & Comparative Immunology, 53 (2), 271–282. doi: 10.1016/j.dci.2015.07.010

[9] Thibeault, S. L., Rees, L., Pazmany, L., Birchall, M. A. (2009). At the crossroads: mucosal immunology of the larynx. Mucosal Immunology, 2 (2), 122–128. doi: 10.1038/mi.2008.82

[10] Bertoni, A. G., Saydah, S., Brancati, F. L. (2001). Diabetes and the Risk of Infection-Related Mortality in the U.S. Diabetes Care, 24 (6), 1044–1049. doi: 10.2337/diacare.24.6.1044

[11] Casteleyn, C., Broos, A. M. C., Simoens, P., Van den Broeck, W. (2010). NALT (nasal cavity-associated lymphoid tissue) in the rabbit. Veterinary Immunology and Immunopathology, 133 (2-4), 212–218. doi: 10.1016/j.vetimm.2009.08.011

[12] Guzik, T. J. (2002). Mechanisms of Increased Vascular Superoxide Production in Human Diabetes Mellitus: Role of NAD(P)H Oxidase and Endothelial Nitric Oxide Synthase. Circulation, 105 (14), 1656–1662. doi: 10.1161/01.cir.0000012748.58444.08

[13] Roux, M. E., del Lopez, M. C., Florin-Christensen, A. (2000). Mucosal Immunity. Probiotics 3, 12–28. doi: 10.1007/978-94-017-2768-6_1

[14] Heritage, Brook, Underdown, McDermott (2001). Intranasal immunization with polymer-grafted microparticles activates the nasal-associated lymphoid tissue and draining lymph nodes. Immunology, 93 (2), 249–256. doi: 10.1046/j.1365-2567.1998.00420.x

[15] Kraal, G. (2005). Nasal-Associated Lymphoid Tissue. Mucosal Immunology, 415–422. doi: 10.1016/b978-012491543-5/50027-9

[16] Sosa, G. A., Roux, M. E. (2004). Development of T Lymphocytes in the Nasal-associated Lymphoid Tissue (NALT) from Growing Wistar Rats. Clinical and Developmental Immunology, 11 (1), 29–34. doi: 10.1080/10446670410001670463

[17] NALT / BALT and Oral Cavity (2009). Mucosal Immunology, 2 (1s). doi: 10.1038/mi.2009.43

[18] Sepahi, A., Salinas, I. (2016). The evolution of nasal immune systems in vertebrates. Molecular Immunology, 69, 131–138. doi: 10.1016/j.molimm.2015.09.008

[19] Hathaway, L. J., Kraehenbuhl, J.-P. (2000). The role of M cells in mucosal immunity. Cellular and Molecular Life Sciences, 57 (2), 323–332. doi: 10.1007/pl00000693

[20] Berger, T. (2008). Tolerability and efficacy of a herbal combination preparation in children and adolescents with recurrent infections of the upper respiratory tract. MMW Fortschr Med., 150, 85–90.

THE CLINICAL FEATURES OF ATRIOVENTRICULAR CANAL DEFECT

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Abstract

Atrioventricular canal defect (AVCD) is a congenital heart defect, which occurs in 2.9 % of all congenital heart defects (CHD) and is characterized by a wide variety of anatomical forms and often don't have clear cardiac manifestation. Untreated AVCD may lead to the development of pulmonary hypertension.

Aim. To determine clinical features of AVCD in children, considering variable anatomical forms of the pathology and its association with genetic pathology.

Materials and methods. Patients history and outpatient statistic records of children with AVCD, who were admitted to Lviv Regional Children's Hospital from September 1999 till January 2016 have been analyzed (n=84).

The aspects of clinical manifestation of AVCD without associated pathology have been identified (n=48). Clinical manifestation of complete (n=36) and incomplete (n=12) AVCD and clinical manifestation with and without Down syndrome have been discussed.

Children with AVCD were divided into two groups: A – children with complete (n=36) and B – with incomplete (n=12) form of AVCD. Group A was divided into A1 – with trisomy 21 (n=14), A2 – without genetic pathology (n=22).

Results. In group A2 – 36,36±10,26 % and in group B – 50±14,4 % children were asymptomatic. Dyspnea, increased sweating during feeds, growth retardation and frequent respiratory viral infections during early childhood period were leading symptoms. Most frequent auscultation findings were accent of II heart sound over the pulmonary artery and 2-3/6 systolic murmur over left sternal border. According to echocardiographic examination mitral valve insufficiency was predominantly of mild grade, tricuspid insufficiency and pulmonary hypertension was diagnosed in group A2 with the frequency of 9,09±6,13 %).

Conclusions: The absence of clinical features in group A2 and B 36,36±10,26 and 50,00±14,40 respectively, saturation levels 92,36±0,49 % in patients without genetic pathology and 95,25±0,40 % with incomplete AVCD provide a need to adopt protocol of children examination with saturation level under 95 % and compulsory echocardiographic diagnosis within the first month of life.

Keywords: Atrioventricular canal defect, complete and incomplete AVCD, trisomy 21, echocardiography, trisomy 21.

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1. Introduction

According to WHO data 4–5 % of the newborns are diagnosed with congenital or hereditary pathology annually [1]. Nearly 2 % of them are diagnosed with severe anomalies inconsistent with life and primarily with congenital heart defects [2]. Almost 40 % of the early childhood mortality partially or completely is caused by hereditary diseases and half of them are the cardiac system pathology [3].

Nearly 28–30 000 children are born in Lviv region annually and nearly 220–280 are diagnosed with CHD [4]. Cardiac defects are among the leading cause of the childhood mortality and disability [5].

2. Aim of research

To determine clinical features of various forms of atrioventricular canal defect (AVCD) in children with and without genetic pathology.

3. Materials and methods

Patients history and outpatient statistic records of the children with AVCD, who were admitted to Lviv Regional Children's Hospital in the period of September 1999 – January 2016 have been analyzed (n=84). Patient history, clinical features, chest X-ray, Ekg and echocardiography data have been included in the research.

Clinical features of the defect were determined in children without associate pathology (n=48). Children were divided into two groups – A – children with complete form of atrioventricular canal defect (n=36), and B – children with incomplete AVCD (n=12). Group A was divided into two groups: A1 – children with complete form of AVCD and trisomy 21 (n=14), A2 – children with complete form and without genetic pathology, respectively (n=22).

Gained results were gathered in the table in absolute numbers with the following mathematical calculation on a personal computer with the "Microsoft Excel" and "Statistica" programs used.

During the medical statistical analysis the mean and its standard deviation (M±σ), relative values, reliability and likelihood differences among analyzed groups were estimated.

The normality check proved Gaussian type distribution data, therefore in the binary comparison the Student's T-criteria, and in frequency comparison – xi-square were applied.

4. Results

According to the research it was determined, that children with AVCD had eight main clinical features. They were most frequently seen in children with complete form and with trisomy 21 (group A1); asymptomatic children were observed in group A2 – B 36,36±10,26 % and 50±14,4 %, respectively (**Table 1**).

Therefore, children with complete form of AVCD and with trisomy 21 (group A1) the most frequently diagnosed clinical features were tachypnea, sweating during feeding (in 100 %), growth retardation (in 78,57±11,00 %), failure to thrive and frequent respiratory tract infections (50,00±13,40 %).

Most frequent clinical features in children with complete form of ACD without genetic pathology (group A2) were failure to thrive (50,00±10,66 %) and growth retardation (40,91±10,48 %), tachypnea and excessive sweating during feeds (36,36±10,26 %).

Children with incomplete form of AVCD 9 group B) most frequently had: recurring respiratory tract infections in their medical history (41,67±14,20 %), tachypnea and excessive sweating during feeds (33,33±13,60 %), and failure to thrive (25,00±12,50 %). Absence of clinical features was seen in group A2 and B – 36,36±10,26 and 50,00±14,40 respectively.

Table 1

Frequency (%) of clinical features in children with AVCD

№	Clinical features	Groups		
		A1	A2	B
1	Tachypnea, excessive sweating during feeds	100	36,36±10,26**	33,33±13,60**
2	Growth retardation	78,57±11,00	40,91±10,48	25,00±12,50**
3	Failure to thrive	50,00±13,40	50,00±10,66	25,00±12,50
4	Recurrent respiratory tract infections	50,00±13,40	27,27±9,50	41,67±14,20
5	Aggravated cardiac heave	21,43±11,00	13,64±7,32	25,00±12,5
6	Cyanosis	14,29±9,40	0	0
7	Enlarged chest cage	7,14±6,90	0	0
8	Heart hump formation	7,14±6,90	0	0
9	Absence of clinical features	0	36,36±10,26**	50,00±14,40**

*Note: ** – reliable (p<0,01) difference is present in comparison with group A1*

Auscultation data was analyzed as well. In children with complete AVCD and trisomy 21 (Group A1) were accentuated second heart sound of the pulmonary artery (PA) (in 71,43±12,10 %) and 2/6 on the Levine scale systolic murmur over the left sternal border (57,14±13,20 %). Children with complete AVCD without genetic pathology (group A2) had the same auscultation findings, although less frequently (**Table 2**).

In children with incomplete form of AVCD the most frequent auscultation findings were – 1-2/6 systolic murmur over the left sternal border (58,33±14,20 %) and a soft second tone accent over the PA (41,67±14,20 %).

Table 2
Auscultation data (%) in children with AVCD

№	Auscultation data	Groups		
		A1	A2	B
1	Systolic murmur over the left upper sternal border	21,43±11,00	36,36±10,26	33,33±13,60
2	Systolic murmur over the left sterna border	57,14±13,20	50,00±10,66	58,33±14,20
3	No auscultation findings	21,43±11,00	0	33,33±13,60
4	1\6	0	27,27±9,50	16,67±10,80
5	2\6	57,14±13,20	40,91±10,48	25,00±12,50
6	3\6	0	13,64±7,32	25,00±12,50
7	4\6	7,14±6,90	0	0
8	S2 accent over PA	71,43±12,10	59,09±10,48	41,67±14,20
9	Holosystolic murmur over the left sternal border	0	4,55±4,44	8,33±8,00

During percussion, reliable ($p<0,01$) in groups of children with complete AVCD – the widening of the heart borders to the right (92,86±6,90 in group A1 and 90,91±6,13 in group A2), in comparisson with the group B, where this indication constituted 41,67±14,20 %. Simultaneously, the widening of the heart borders to the left most frequently was seen in children with incomplete form of AVCD, however there was no reliable difference in those parameters in groups of children with complete AVCD (**Table 3**).

Table 3
Percussion data (%) in children with AVCD

№	Percussion data	Groups		
		A1	A2	B
1	Widening to the right	92,86±6,90 ₤₤	90,91±6,13 ₤₤	41,67±14,20
2	Widening to the left	0	4,55±4,44	8,33±8,00

Note: ₤₤ – reliable difference ($p<0,01$)is present in comparison with group B

It was established that the middle level of the saturation (**Fig. 1**) was reliably (p<0,01) lower in group of children with complete AVCD and with trisomy 21 and constituted 88,00±2,30 %. In patients without genetic pathology it was in the range of 92, 36±0,49 %, and in children with incomplete AVCD – 95,25±0,40 %.

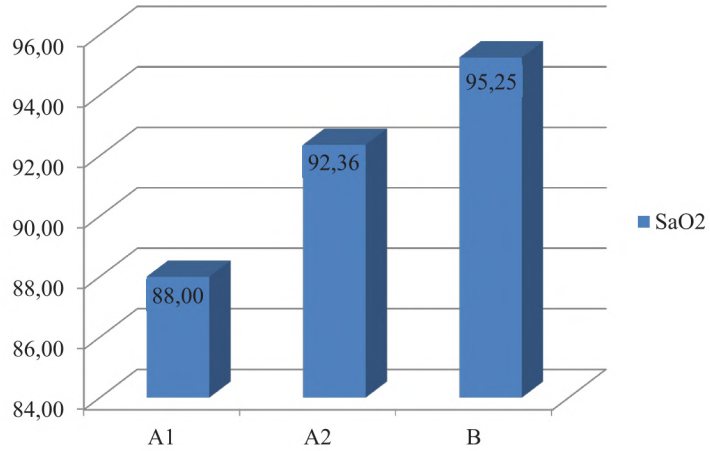

Fig. 1. Average saturation levels (%) in children within three groups in children with AVCD

During the analysis of internal organs ultrasound − no pathology was diagnosed. Rarely (9 %) it was combined with lowered and horseshoe kidney and hepatomegaly. It is worth mentioning that only children without associated pathology were included into the research. Therefore AVCD was not associated with any internal pathology in our research (**Table 4**).

Table 4

Internal organs ultrasound data (%) in children with AVCD

№	Ultrasound data	Groups		
		A1	A2	B
1	No pathological findings	100	90,91±6,13	91,67±8
2	Lowered right kidney	0	0	8,33±8
3	Horseshoe kidney	0	4,55±4,44	0
4	Hepatomegaly	0	4,55±4,44	0

According to EKG data, sinus rhythm was present in all groups and only in the group of children with complete AVCD without genetic pathology 4,55±4,44 % the first degree heart block was diagnosed. The right bundle branch block was diagnosed in − 33,33 ±13,60 % in the group of children with incomplete AVCD (**Table 5**).

According to Echocardiography data in children with complete AVCD associated with trisomy 21 − 78,57±11,00 % prevailed balanced form and in the group without genetic pathology (A2) balanced form was met in 90,91±6,13 % of children.

In **Table 6** it is shown that pulmonary hypertension was more frequently diagnosed in the group A1, however the IV stage of PH was diagnosed in 9,09±6,13 % children with complete form of AVCD without genetic pathology.

Table 5
EKG findings (%) in children with AVCD

№	EKG findings	Groups		
		A1	A2	B
1	Sinus rhythm	100	95,45±4,44	100
2	I-st degree AV block	0	4,55±4,44	0
3	Leftward axis deviation	100	95,45±4,44	91,67±8,00
4	Rightward axis deviation	0	4,55±4,44	8,33±8,00
5	Right heart chambers hypertrophy	100	95,45±4,44	100
6	RBBB	14,29±9,40	13,64±7,32	33,33±13,60

Table 6
Echocardiography data (%) in children with AVCD

№	Echocardiography data	Groups		
		A1	A2	B
1	I degree PH	14,29±9,4	13,64±7,32	8,33±8,00
2	II degree PH	35,71±12,80	4,55±4,44	0
3	III degree PH	7,14±6,90	0	0
4	IV degree PH	0	9,09±6,13	0
5	Right chambers volume overload	92,86±6,90	68,18±9,93*	33,33±13,60**#
6	ASD I (mm)	8,93±1,00	9,55±0,73	11,67±1,30
7	VSD	9,21±1,40	5,05±0,63#	5,50±2,50
8	Bulging aneurysm	0	0	8,33±8,00
9	Single av valve	28,57±12,10	13,64±7,32	0*
10	Unique atrium	7,14±6,90	0	0
11	AV valve insufficiency	7,14±6,90	9,09±6,13	0
12	Clefted anterior mitral leaflet	64,29±12,80	68,18±9,93	100*#
13	Mitral valve insufficiency 1+ (mild)	78,57±11,00	77,27±8,93	66,67±13,60
14	Mitral valve insufficiency 2+ (moderate)	7,14±6,90	9,09±6,13	8,33±8,00
15	Mitral valve insufficiency 3+ (severe)	0	0	8,33±8,00
16	Tricuspid valve insufficiency 1+ (mild)	28,57±12,10	31,82±9,93	0*#
17	Tricuspid valve insufficiency 2+ (moderate)	0	4,55±4,44	8,33±8,00
18	Single atrium	14,29±9,40	0	0
19	Deformed anterior leaflet	0	4,55±4,44	0
20	Aorta (cm)	1,22±0,10	1,41±0,09	1,46±0,10
22	Pulmonary Artery (cm)	1,41±0,10	1,51±0,08	1,53±0,10
23	EF %	70,07±0,90	69,18±0,81	69,58±0,50

*Note: * – reliable difference (p<0,05) in comparison with group A1; ** – reliable difference (p<0,01) in comparison with group A1; # – reliable difference (p<0,05) in comparison with group A2; ## – reliable difference (p<0,01)in comparison with group A2*

Insignificant (p<0,05) right chambers volume overload was diagnosed in children with incomplete AVCD (33,33±13,60 %), whereas in children with complete AVCD − 68,18±9,93 % in group A2 and in 92,86±6,90 % − in group A1.

Single AV valve was not diagnosed in children with incomplete AV canal, whereas (100 %) had clefted anterior mitral valve leaflet.

Mild mitral valve insufficiency was diagnosed in all groups, whereas moderate and severe was observed much rarely. Mild tricuspid insufficiency in groups with complete form of AVCD prevailed in the A2 group; moderate tricuspid insufficiency was met in the group A2 and B.

According to the chest x-ray data, the aggravation of the pulmonary fields, widened vascular bundle and widened PA is more common for all groups of children with CAVCD (**Table 7**).

Table 7

Chest X-ray data (%) in children with AVCD

№	Chest x-ray data	Groups		
		A1	A2	B
1	Cardiomegaly	28,57±12,10	13,64±7,32	8,33±8,00
2	increased pulmonary pattern	100	100	91,67±8,00
3	Pulmonary fields without focal and infiltrative shadows	0	0	8,33±8,00
4	Overlapping PA	14,29±9,40	4,55±4,44	0
5	KTI %	55,86±1,00	55,41±1,05	53,18±1,10
7	Unchanged vascular bundle	0	0	8,33±8,00
8	Widened vascular bundle	100	90,91±6,13	58,33±14,20*#
9	Flattened waist of the heart	0	0	8,33±8,00

*Note: * – present reliable (p<0,05) difference in comparison with the subgroup A1; # – present reliable (p<0,05) difference in comparison with subgroup A2*

5. Discussion

According to the official data, the amount of congenital heart defects has increased significantly as well as its role in the cause of the newborn mortality. Congenital heart defects are the reason of the newborn mortality in 15 % of the cases [6]. Nearly 40 % of the children with congenital heart defects die without surgery, and nearly 70 % of them die during the first days of life and the 30 % die during the first year of life, respectively [7].

AVCD constitutes 3−5 % in the structure of all of the congenital heart defects [7−9], however according to fetal echo-cardiography the frequency of AVCD may be up to 17 % [10]. Heterotaxy syndrome is combined with AVCD in 80 % (more frequently asplenia rather then polysplenia [2, 3]. Children with trisomy 21 have congenital heart defect and in 40 % of the cases it is AVCD (the complete form prevails) [3, 6, 10]. According to the molecular mapping it is considered that the part of the 21-st chromosome 21q22.1-qter could be linked to the impairment of the endocardial cushions development [6, 11].

AVCD is characterized by a wide variety of its anatomical forms and as a rule, does not have a typical for a congenital heart defect early clinical manifestation [12]. This contributes to the difficulties of early clinical diagnosis of the following CHD, which is crucial in terms of definition of the terms of the surgical correction of the defect [13].

Parents of the most of children with AVCD do not have any complaints, therefore the disease can be suspected by a pediatrician during the random visit for a checkup. Depending on a size of VSD doctor could auscultate 1-3/6 systolic murmur over the left sternal border and a typical Ekg should be helping in diagnosing this defect [14, 15].

AVCD – is a complex congenital heart defect which is characterized by the anomalous connection on the ventricular and atrial level due to the common atrioventricular canal, which occurs due to the endocardial cushions defect [16, 17]. In the process of embryogenesis endocardial cushions form two atrioventricular valves and participate in the end stage of the septum formation. Therefore the defect of the embryogenesis caused by different factors leads to septal and two separate valve (mitral and trileaflet) and cusps formation defection [18–20].

6. Conclusions

1. Children with AVCD are not often manifested clinically, and the risk of developing pulmonary hypertension is high, the necessity of creating a protocol of clinical diagnosis of this congenital heart defect is well-grounded.

2. Echocardiography remains a golden standard of diagnosis of AVCD, especially in children with trisomy 21.

3. Saturation level has to be checked at the maternity hospital. Children with the saturation level lower than 95 % have to undergo echocardiography examination in the early neonatal period.

References

[1] Calabro, R., Limongelli, G. (2006). Complete atrioventricular canal.Orphanet Journal of Rare Diseases, 1 (1), 8. doi: 10.1186/1750-1172-1-8

[2] Allen, H. D., Driscoll, D. J., Shaddy, R. E., Feltes, T. F. (2008). Moss and Adam's Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults. Philadelphia: Lippincott Williams & Wilkins, 1680.

[3] Crawford, M. H., DiMarco, J. P., Paulus, W. J. et. al. (2010). Cardiology. Mosby. Ch. 117. Atrioventricular Canal Defects, 1561–1571.

[4] Main Administration of the Statistics in Lviv Region (2015). Statistic data. Report «Population 1995-2015 year», 1.

[5] Hoffman, J. I., Kaplan, S. (2002). The incidence of congenital heart disease. Journal of the American College of Cardiology, 39 (12), 1890–1900. doi: 10.1016/s0735-1097(02)01886-7

[6] Abdulla, R. (2011). Heart Diseases in Children: A Pediatrician's Guide. Berlin: Springer, 123–132. doi: 10.1007/978-1-4419-7994-0

[7] Anderson, R. H., Baker, E. J., Penny, D., Redington, A. N., Rigby, M. L., Wernovsky, G. (2010). Paediatric Cardiology. Ch. 8-9. Amsterdam: Elsevier Ltd., 1327. doi: 10.1016/b978-0-7020-3064-2.00073-4

[8] Acar, P., Laskari, C., Rhodes, J., Pandian, N., Warner, K., Marx, G. (1999). Three-dimensional echocardiographic analysis of valve anatomy as a determinant of mitral regurgitation after surgery for atrioventricular septal defects. The American Journal of Cardiology, 83 (5), 745–749. doi: 10.1016/s0002-9149(98)00982-5

[9] Barnett, J. V., Desgrosellier, J. S. (2007). TGFβ Signaling During Atrioventricular Cushion Transformation. Ch. 13. Cardiovascular Development and Congenital Malformations, 55–58. doi: 10.1002/9780470988664.ch13

[10] Lymarenko, M. P., Logvynenko, N. G., Artyuch, T. V. (2009). Atriovantricular communication as a most frequent defect in children with Down Syndrome. Ukrainian cardiology journal, 4, 77–81.

[11] Baron, M. G., Wolf, B. S., Steinfeld, L., Van Mierop, L. H. S. (1964). Endocardial cushion defects. The American Journal of Cardiology, 13 (2), 162–175. doi: 10.1016/0002-9149(64)90171-7

[12] Bonow, R. O., Carabello, B. A., Chatterjee, K., de Leon, A. C., Faxon, D. P., Freed, M. D. et. al. (2006). ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. Journal of the American College of Cardiology, 48 (3), e1–e148. doi: 10.1016/j.jacc.2006.05.021

[13] Hoohenkerk, G. J., Bruggemans, E. F., Rijlaarsdam, M., Schoof, P. H., Koolbergen, D. R., Hazekamp, M. G. (2010). More than 30 years' experience with surgical correction of atrioventricular septal defects. The Annals of Thoracic Surgery, 90 (5), 1554–1561. doi: 10.1016/j.athoracsur.2010.06.008

[14] Ongley, P. A., Pongpanich, B., Spangler, J. G., Feldt, R. H.; Feldt, R. H. (Ed.) (1976). The electrocardiogram in atrioventricular canal. Atrioventricular canal defects. Philadelphia: WB Saunders, 51.

[15] Barratt-Boyes, B. G., Neutze, J. M., Harris, E. A. (Eds.) (1973). Correction of atrioventricular canal defects in infancy using profound hypothermia. In Heart disease in infancy: diagnosis and surgical treatment. Edinburgh: Churchill Livingstone, 110.

[16] Cheng, H.-L., Huang, C.-H., Tsai, H.-E., Chen, M.-Y., Fan, S.-Z., Hsiao, P.-N. (2012). Intraoperative Assessment of Partial Atrioventricular Septal Defect with a Cleft Mitral Valve by Real-Time Three-Dimensional Transesophageal Echocardiography. Anesthesia & Analgesia, 114 (4), 731–734. doi: 10.1213/ane.0b013e3182468db3

[17] Machlitt, A., Heling, K.-S., Chaoui, R. (2004). Increased cardiac atrial-to-ventricular length ratio in the fetal four-chamber view: a new marker for atrioventricular septal defects. Ultrasound in Obstetrics and Gynecology, 24 (6), 618–622. doi: 10.1002/uog.1750

[18] Jegatheeswaran, A., Pizarro, C., Caldarone, C. A., Cohen, M. S., Baffa, J. M., Gremmels, D. B. et. al. (2010). Echocardiographic definition and surgical decision-making in unbalanced atrioventricular septal defect: a Congenital Heart Surgeons' Society multiinstitutional study. Circulation, 122 (11), S209–S215. doi: 10.1161/circulationaha.109.925636

[19] Kogon, B. E., Butler, H., McConnell, M., Leong, T., Kirshbom, P. M., Kanter, K. R. (2007). What is the optimal time to repair atrioventricular septal defect and common atrioventricular valvar orifice? Cardiology in the Young, 17 (04), 356. doi: 10.1017/s1047951107000856

[20] Lacour-Gayet, F., Comas, J., Bruniaux, J., Serraf, A., Losay, J., Petit, J. et. al. (1991). Management of the left atrioventricular valve in 95 patients with atrioventricular septal defects and a common atrioventricular orifice–a ten year review. Cardiology in the Young, 1 (04), 367–373. doi: 10.1017/s104795110001043x

THE RARE REGULAR TRISOMY 17: FREQUENCY AND PHENOTYPIC PORTRAIT

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Abstract

This paper presents the data from our own research of frequency of full regular trisomy 17 (T17) based on 1808 samples of miscarriages, 1572 medical induced abortions at 5–11 weeks of gestation, and 9689 samples of invasive prenatal tests done between 11 and 24 weeks of pregnancy. The frequency of full T17 in all miscarriages was 1/152 and in medical induced abortions – 1/524; the population frequency of T17 in the first trimester accounted for 1/454.

Additionally, it presents the data on the proportion of T17 of all autosomal trisomies structure in different periods of fetal development. When performing invasive prenatal testing we detected 4 cases of T17 that represented 0,58 % of autosomal trisomies among fetuses of 11–22 gestational weeks.

Furthermore, the paper introduces a symptom-complex of fetal abnormalities that are typical of regular full trisomy 17.

Keywords: chromosomal abnormalities, trisomy 17, rare trisomies, miscarriages, ultrasound prenatal diagnostics.

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1. Introduction

Chromosomal abnormalities (CA), whose frequency makes up 50–60 % of early reproductive losses and due to the natural mortality rate goes down to 0.5–0.7 % of live births, holds a specific place in the structure of congenital and hereditary diseases.

Trisomies constitute the largest proportion of all chromosomal abnormalities.

Over the past 40 years, or even more, there have been performed only a few large-scale studies in which the number of karyotype sample from missed abortions exceeded 1,000 specimen of non-developing products of concept [1–4]. While these studies were carried out at different times in different countries and populations, in all of them trisomy prevailed in the structure of chromosomal abnormalities found in missed pregnancies, with its portion varying from 44 to 66 % (**Table 1**).

Table 1

The study of first trimester miscarriages karyotypes

	Boue 1975	**Hassold 1980**	**Kline 1987**	**Menasha 2005**
Total analyzed	1498	1000	2098	1203
Total anomalies	921 (61,5 %)	463 (46,3 %)	776 (37,6 %)	792 (65,8 %)
Trisomy	479 (52,0 %)	207 (44,5 %)	368 (47,4 %)	522 (65,9 %)

The analysis has shown unequal participation of different chromosomes in the structure of autosomal trisomies. Trisomies 21, 18 and 13 in newborn infants generally account for 95 % of chromosomal abnormalities. In the earlier stages of fetal development, this rate is lower. Therefore it is assumed that all trisomies, except 21, 18, and 13, are rare.

Rare trisomies should be a key focus, since phenotype of fetuses with such abnormalities is not yet described for their low frequency. Until now it has been believed that trisomy 1 and trisomy 19 are incompatible with postimplantation development [5].

Our research experience over the last 20 years proves that there is a whole spectrum of autosomal trisomies (including such rare ones as regular trisomies 1 and 19) in the structure of early reproductive losses of first trimester.

The analysis of frequency of rare trisomies detected in the process of prenatal diagnosis at 11–26 weeks (early and middle periods of fetal development) has shown a large proportion of T8, T9, T22, T14, T16, T20, T17 and T15 in the structure of prenatally diagnosed abnormalities, but of all those mentioned only T8, T9, T22 have been classified into separate syndromes [6].

Special mention in this context should be made of the cases of full regular trisomy 17. In known reputable sources, directories, guides, manuals, and electronic databases (PubMed, Medline, OMIM) we have not found any description of phenotype for fetus with regular trisomy 17 (only cases of mosaic trisomies 17 are specified) [7, 8].

2. Aim of research

To determine the frequency and mortality of regular trisomy 17 based on the cases we were fixing through our multi-year research, and to describe a symptom- complex of fetal abnormalities that are typical for regular full trisomy 17.

3. Materials and Methods

To meet our targets for the period of 1997 through 2016, we formed groups and made karyotyping of 1808 samples of miscarriages concept products, randomized group of 1572 medical induced abortions at 5–11 weeks of gestation; 9689 samples of invasive prenatal tests done between 11 and 24 weeks of pregnancy (1329 chorionic villus biopsies, 2240 placental biopsies, and 6120 samples of amniotic fluid) - total 13069 samples from women inhabiting south-east and central regions of Ukraine.

Prenatal ultrasound examinations were performed in the 1-st trimester pregnancy to identify the missed miscarriage, as well as in the periods of 11–14 weeks and 18–22 weeks of gestation with ultrasound systems HDI-3000 “ATL/Philps” (USA) and Voluson 730-Pro “General Electric” (USA). Prenatal invasive procedures were controlled using ultrasound scanners SSA-250 “Toshiba” (Japan) and R-3 “Samsung-Medison” (Korea). After elimination of abnormal fetuses with chromosomal aneuploidy, autopsy of abortus was done.

For the analysis we applied GTG (method for differential staining), and we used research microscopes Axioimager A1 “Zeiss”, “Olimpus” BX41, Aristoplan “Leitz” to analyze chromosome spreads . Notice also that we met testing standard for chromosome spreads [9], evaluating no less than 30 metaphase plates.

4. Results

We have found that the proportion of T21, 18, and 13 in pre-embryonic period generally accounts for only 6.33 %, while that of rare trisomy – 93.67 %. Among pregnancies terminated in embryonic period of 5 to 11 weeks, the proportion of rare autosomal trisomies made up 88.2 %. In early fetal period of 11–14 gestational weeks, the rare autosome trisomies amounted to only 6.9 %; at 15–22 weeks – 3.83 %; after 23 weeks – 6.68 % (i. e., the average proportion of rare autosomal trisomies in the fetal group of early, middle and late period made 5.8 %).

The frequency of full T17 in all miscarriages was 1/152 and in medical induced abortions – 1/524; the population frequency of T17 in the first trimester accounted for 1/454. In the process of study we have found that the proportion of trisomy 17 in autosomal trisomy structure varies in different periods of fetal development (**Table 2**).

Specifically, in the group of first trimester miscarriages, T17 proportion averaged 1. 17 %. There were recorded 6 cases of full regular T17 (1 of anembryonic gestation and 5 with embryos which stopped growing), and 2 cases of mosaic T17 combined with polyploidy (one of them with double T17, karyotype: 94, XXXX, +17+17/47, XX+17 mos, the second one – with karyotype: 70, XXX+17/ 47, XX+17 mos) both of anembryonic gestation. In all these cases, pregnancy stopped developing at 5–9 weeks. When performing prenatal testing, we revealed 4 cases of trisomy 17 (**Table 3**) that represented 0.58 % of autosomal trisomies among fetus of 11–22 gestational weeks.

Table 2

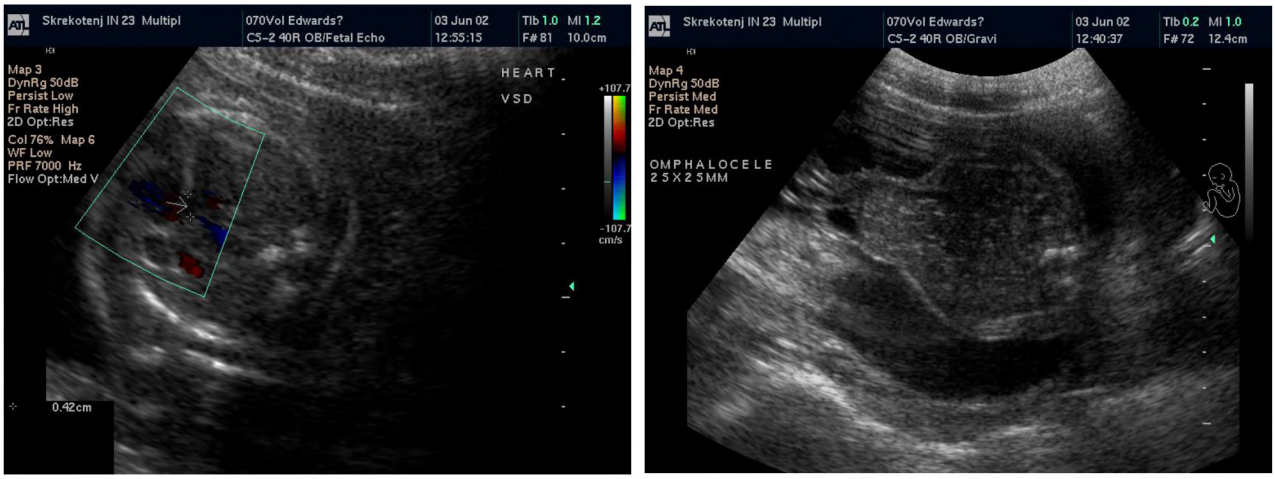
Proportion of T17 in structure of autosomal trisomies in different periods of fetal development

Chromosomal abnormality	Miscarriages Pre-embryonic stage (prior 5 weeks)	Miscarriages 5–11 wks	Prenatal diagnostic 11–14 wks	Prenatal diagnostic 15–22 wks
Trisomy +17	1 (0,79 %)	5 (1,53 %)	1 (0,43 %)	3 (0,72 %)

Table 3

Features of pregnancy with prenatally detected trisomy 17

№	Maternal age	Gestational age (wks)	Ultrasound findings	Karyotype
1	23	22	Prenatal hypoplasia, ventricular septal defect, 'lemon'-shaped head, omphalocele, flexor position of hand, 'rocker-bottom' foot, umbilical cord cyst (**Fig. 1, *a, b***)	47,XX+17
2	17	19-20	Prenatal hypoplasia, nasal bone hypoplasia, brachycephaly.	47,XY+17
3	24	11	Exencephaly,omphalocele,spine deformation and shortening, feet deformation (**Fig. 2**)	47,XY+17 (**Fig. 3**)
4	24	20	Prenatal hypoplasia, severe hydrocephalus, facial dismorphism, nasal bone hypoplasia, complicated cardiac defect, abnormal limbs length (bilateral talipomanus, radial bone aplasia, flexion deformity of hand, unilateral abnormality of lower limb, fibula bone aplasia) spine deformity, small-sized omphalocele (**Fig. 4, *a–e***)	47,XY+17



a *b*

Fig. 1. Echograms of fetus with the full trisomy 17 at 22 weeks of gestation:
a − Transaxial section through the fetal thorax and heart (four-chamber view), ventricular septal defect; *b* − Transaxial section through the fetal abdomen; anterior wall defect: omphalocele

In one case (№ 3) a fetus had severe malformations (**Fig. 2**), similar to ADAM-complex (sequence of amniotic bands), but meticulous ultrasound screening did not detect any manifestations of amniotic bands. Given these abnormalities, there were performed a prenatal differential diagnosis for thoracoabdominal syndrome, OEIS-complex (omphalocele-extrophy-imperforate anus − spinal defects), and with less potential trisomies of chromosomes 18 and 13 that necessitated the prenatal karyotyping which revealed the trisomy 17 (**Fig. 3**).

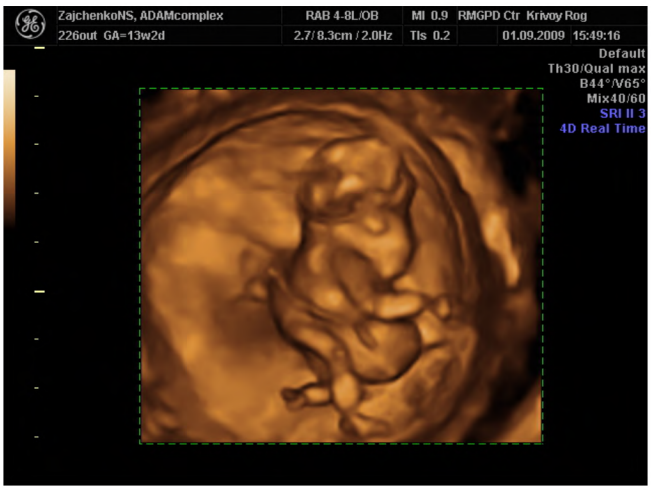


Fig. 2. 3D echography surface reconstruction of the fetus with the full trisomy 17 at 11 weeks of gestation. Multiple congenital anomalies: exencephaly, omphalocele, spine shortening and deformation, feet deformation

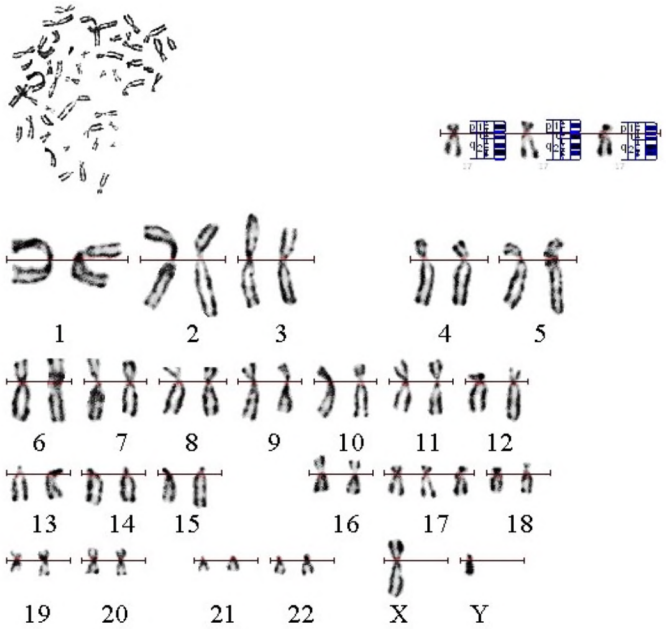


Fig. 3. Karyogram of the fetus at 11 weeks of gestation in Chorionic villus sampling material: 47, XY + 17 (10X100 increase; software "Video Test Karyo 3.1")

In one case (№ 4) the prenatal differential diagnosis was made with TAR syndrome, which had been excluded, because the fetus had no manifestations of anemia. In addition to fetal abnormalities detected by ultrasound (**Fig. 4, *a*–*e***) and later confirmed by autopsy (**Fig. 5, *a, b***), there have been also found such dysmorphic disorder of face as hypertelorism, horizontal eye slits, wide and deep nasal bridge, and mild retromicrognathia.

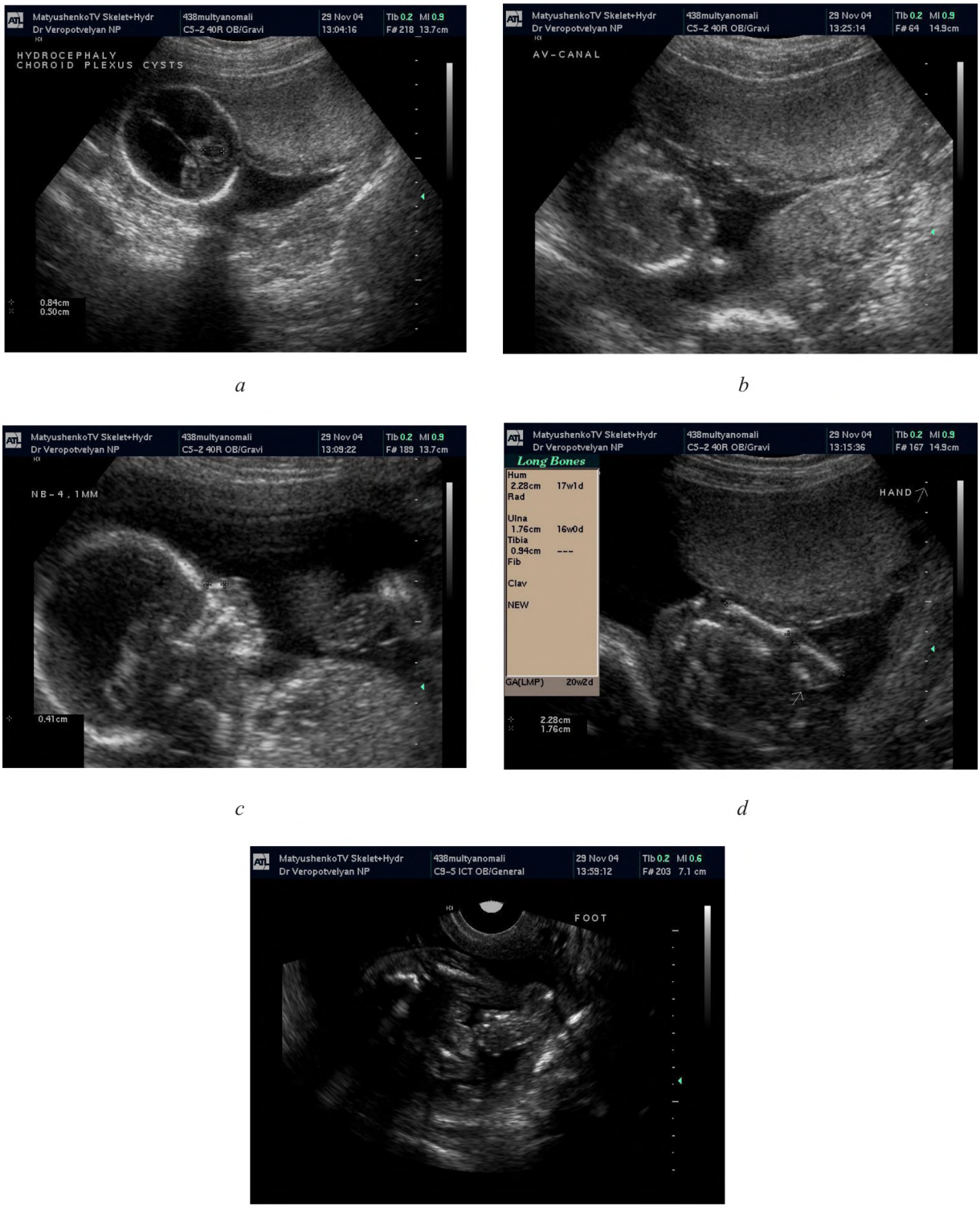
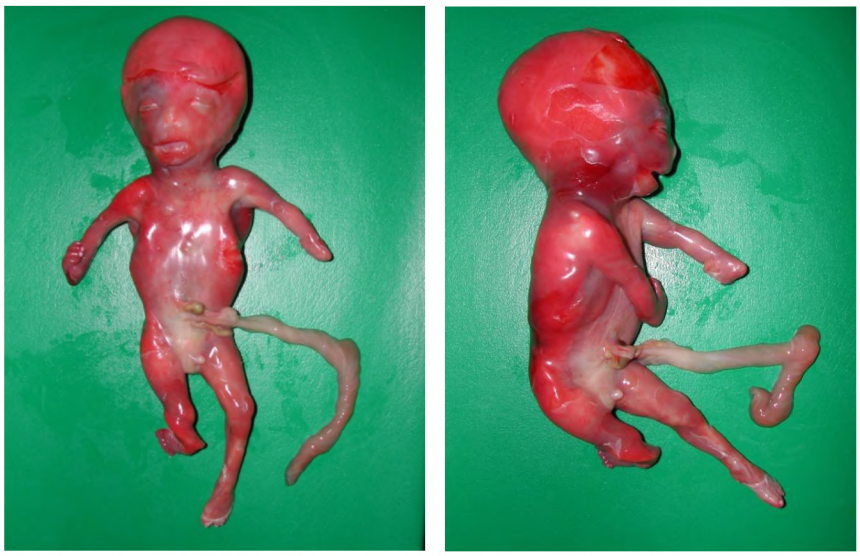


Fig. 4. Echograms of fetus with the full trisomy 17 at 20 weeks of gestation:
a − transaxial section through the fetal head: hydrocephaly, choroid plexus hypoplasy and cysts;
b − Transaxial section through the fetal thorax and heart. Abnormal four-chamber view:
horisontal cardiac axis,complete atrio-ventricular channel; *c* − sagittal section of the fetal face:
high forehead,deep nasal bridge, nasal bone hypoplasia, mild microretrognathy;
d − sagittal section through the fetal upper limb: radiation clubhand, due to radial bone aplasy;
e − transverse section of the deformed foot



a *b*

Fig. 5. Aborted fetus with the full trisomy 17 at 21 weeks of gestation. (Phenotype description in the text): *a* – front view; *b* – side view

Based on ultrasound and postmortem examinations, we have formed a symptom-complex of abnormalities which are typical of full regular trisomy 17 (**Table 4**).

Table 4

Symptom-complex of abnormalities which are typical of full regular trisomy 17

Anatomo-morphological structures	Anomalies/features
Shape of the head	Brachycephalic (1) 'Lemon' (1)
Central nervous system	Exencephaly (1) Hydrocephalus (1) Cerebellum hypoplasy (1)
Facial dismorphism	Hyperthelorism (1) horizontal eye slits (1) wide nasal bridge (1) nasal bone hypoplasia (2) retromicrognathy (1)
Heart	Atrio-ventricular channel (1) Ventricular septal defects (1)
Anterior abdominal wall	Omphalocele (3)
Spinal column	Shortening and deformity (1)
Limbs – tubular bones	Bilateral aplasia of the radial bones (1) &unilateral fibula aplasia (1)
Hands and feet	Flexion deformity (2/3)
Fetal growth (bioparameters)	Prenatal hypoplasia: retardation from gestational age (3)
Umbilical cord	Cyst (1)

As can be seen from the nature of the anomalies we have specified in the recorded cases, complete trisomy 17 is characterized by multiple non-inducing each other development abnormalities in the different anatomo-morphological systems which are derived from ectoderm and mesoderm, that allows us to regard the described symptom-complex as a syndrome.

5. Discussion

Full regular T17 fall within lethal AD and have never been observed among born-alive infants, that is also agrees with Hsu L. Y's findings on T17 being found only among spontaneous abortions with 0.1 %-frequency [10].

Worldwide scientific literature points to descriptions of only 29 prenatally diagnosed cases of mosaic T17, of which only 9 (31.03 %) had abnormal ultrasound findings correlated with a high percentage of mosaic trisomic clones in cell culture of amniotic fluid that ranged from 23 % to over 50 % [8].

All these cases had adverse pregnancy outcomes and included the following ultrasound findings: fetal growth delay (prenatal hypoplasia), cerebellar hypoplasia and/or cerebellar vermian hypoplasia, ventriculomegaly, nuchal cystic hygroma, nuchal thickening, congenital heart disease (ventricular septal defect), pleural effusions (hydrothorax), vertebral anomaly, abnormal limb length, foot deformity, and single umbilical artery. Among postnatal findings, in most cases, there were also described hypoplasia of cerebellum, facial dismorphism, ventricular septal defect, body asymmetry and tibial length differences, in two cases – inguinal hernia and postaxial polydactyly, by one case of kyphoscoliosis, duodenal atresia, intestinal malrotation, cardiomyopathy, ventriculomegaly and hydrocephalus. Further, in some cases were recorded neuropsychiatric development, peripheral neuropathy, hearing and vision loss, and growth delay. Life expectancy of children with mosaic trisomy 17 ranged from 9 days to 9 years. Baltensperger A. produced a summary of pre- and postnatally described all phenotypic signs and symptoms of mosaic T17 with some additional features from their own observation over this chromosome [7]. According to these and other authors [7, 8], big differences in phenotypic features of fetus and infants with mosaic T17 should be explained by different percentage of mosaic abnormal cell clones, their different presence in a variety of anatomical and morphological tissue and moderate-sized sample of observations. As noted above, in most cases of mosaic T17 described in various sources, there were no anomalies both in pre- and postnatal period, and they all ended with a natural birth [8].

In such cases, to confirm mosaic T17, complementary to chromosomal analysis of amniotic fluid cultures, there was performed a cytogenetic analysis of blood lymphocytes and fibroblasts of neonates that recognized as 'gold' standard, [7]. However, the level of mosaicism varies greatly in different tissues and does not correlate with prognosis [11–20]. Molecular genetic analysis has confirmed mosaic T17 in several cases resulted from postzygotic mitotic errors in distribution of maternal chromosome 17 [13, 16, 18]. Parental origin of extra chromosome 17 was determined with genome-wide SNP-microarray molecular genetic analysis [11].

The phenotypic portrait of fetuses with full regular T17 that we described also included prenatal hypoplasia, hypoplasia of cerebellum, facial dysmorphism, hydrocephalus, heart septal defect, abnormal spine, asymmetric abnormalities of long bones, and foot deformities. But the distinctive feature of symptom-complex of full T17 in our description is the presence of omphalocele in 3 of 4 fetuses and umbilical cord cyst in one of them. Thus, the detected signs allowed us to describe a phenotypic portrait of previously undescribed syndrome of full trisomy 17.

6. Conclusions

1. Frequency of full trisomy 17 in all miscarriages was 1/152 and in medical induced abortions − 1/524; the population frequency of T17 in the first trimester accounted for 1/454.

2. Trisomy 17 represented 1,17 % of all autosomal trisomies among embryos at 5−11 gestational weeks and 0,58 % only of autosomal trisomies among fetuses of 11−22 gestational weeks.

3. The symptom-complex of regular full trisomy 17 second trimester fetuses includes central nervous system anomalies, facial dismorphism, cardiac septal defects, omphalocele, limbs anomalies, prenatal hypoplasia, and asymmetry.

References

[1] Boue, J., Boue, A., Lazar, P. (1975). Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. Teratology, 12 (1), 11–26. doi: 10.1002/tera.1420120103

[2] Kline, J., Stein, Z. (1987). Epidemiology of Chromosomal Anomalies in Spontaneous Abortion: Prevalence, Manifestation and Determinants. Spontaneous and Recurrent Abortion. Chicago: Oxford Blackwell Scientific, 29–50.

[3] Menasha, J., Levy, B., Hirschhorn, K., Kardon, N. B. (2005). Incidence and spectrum of chromosome abnormalities in spontaneous abortions: New insights from a 12-year study. Genetics in Medicine, 7 (4), 251–263. doi: 10.1097/01.gim.0000160075.96707.04

[4] Hassold, T., Chen, N., Funkhouser, J., Jooss, T., Manuel, B., Matsuura, J. et. al. (1980). A cytogenetic study of 1000 spontaneous abortions. Annals of Human Genetics, 44 (2), 151–164. doi: 10.1111/j.1469-1809.1980.tb00955.x

[5] Jacobs, P. A., Hassold, T. J. (1995). The Origin of Numerical Chromosome Abnormalities. Advances in Genetics, 33, 101–133. doi: 10.1016/s0065-2660(08)60332-6

[6] Vorsanova, S. G., Yurov, Y. B., Chernyshov, V. N. (1999). Chromosomal syndromes and anomalyii. Classification and nomenclature, 192.

[7] Baltensperger, A., Haischer, G., Rohena, L. (2016). Rare case of live born with confirmed mosaic trisomy 17 and review of the literature. Clinical Case Reports, 4 (4), 420–424. doi: 10.1002/ccr3.397

[8] Chen, C.-P., Wang, L.-K., Chern, S.-R., Chen, Y.-N., Chen, S.-W., Wu, P.-S. et. al. (2016). Mosaic trisomy 17 at amniocentesis: Prenatal diagnosis, molecular genetic analysis, and literature review. Taiwanese Journal of Obstetrics and Gynecology, 55 (5), 712–717. doi: 10.1016/j.tjog.2016.07.006

[9] Shaffer, L., McGovan-Jordan, J., Schmid, M. (Eds.) (2013). ISCN 2013: An international System for Human Cytogenetic Nomenclature. Basel: Karger, 140.

[10] Hsu, L. Y., Yu, M. T., Neu, R. L., Van Dyke, D. L., Benn, P. A., Bradshaw, C. L. et. al. (1997). Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20 and 21: karyotype / phenotype correlations. Prenatal Diagnosis, 17 (3), 201–242. doi: 10.1002/(sici)1097-0223(199703)17:3<201::aid-pd56>3.0.co;2-h

[11] De Vries, F. A. T., Govaerts, L. C. P., Knijnenburg, J., Knapen, M. F. C. M., Oudesluijs, G. G., Lont, D. et. al. (2013). Another Rare Prenatal Case of Post-Zygotic Mosaic Trisomy 17. American Journal of Medical Genetics Part A, 161 (5), 1196–1199. doi: 10.1002/ajmg.a.35867

[12] Hassold, T. (1982). Mosaic trisomies in human spontaneous abortions. Human Genetics, 61 (1), 31–35. doi: 10.1007/bf00291327

[13] Daber, R., Chapman, K. A., Ruchelli, E., Kasperski, S., Mulchandani, S., Thiel, B. D. et. al. (2011). Mosaic trisomy 17: Variable clinical and cytogenetic presentation. American Journal of Medical Genetics Part A, 155 (10), 2489–2495. doi: 10.1002/ajmg.a.34172

[14] Genuardi, M., Tozzi, C., Pomponi, M. G., Stagni, M. L., Della Monica, M., Scarano, G. et. al. (1999). Mosaic trisomy 17 in amniocytes: phenotypic outcome, tissue distribution, and uniparental disomy studies. European Journal of Human Genetics, 7 (4), 421–426. doi: 10.1038/sj.ejhg.5200333

[15] Lesca, G., Boggio, D., Bellec, V., Magaud, J. P., Till, M. (1999). Trisomy 17 mosaicism in amniotic fluid cells not found at birth in blood but present in skin fibroblasts. Prenatal Diagnosis, 19 (3), 263–265. doi: 10.1002/(sici)1097-0223(199903)19:3<263::aid-pd506>3.0.co;2-0

[16] Shaffer, L., McCaskill, C., Hersh, J., Greenberg, F., Lupski, J. (1996). A clinical and molecular study of mosaicism for trisomy 17. Human Genetics, 97 (1), 69–72. doi: 10.1007/bf00218835

[17] Terhal, P., Sakkers, R., Hochstenbach, R., Madan, K., Rabelink, G., Sinke, R., Giltay, J. (2004). Cerebellar hypoplasia, zonular cataract, and peripheral neuropathy in trisomy 17 mosaicism. American Journal of Medical Genetics, 130A (4), 410–414. doi: 10.1002/ajmg.a.30124

[18] Utermann, B., Riegel, M., Leistritz, D., Karall, T., Wisser, J., Meisner, L. et. al. (2006). Pre- and postnatal findings in trisomy 17 mosaicism. American Journal of Medical Genetics Part A, 140A (15), 1628–1636. doi: 10.1002/ajmg.a.31319

[19] Bullerdiek, J., Bartnitzke, S. (2008). Hypotonic treatment in visual and automatic chromosome analysis. Clinical Genetics, 22 (3), 150. doi: 10.1111/j.1399-0004.1982.tb01427.x

[20] Collado, F. K., Fisher, A. J., Bombard, A. T. (2003). Counseling patients with trisomy 17 mosaicism found at genetic amniocentesis. Prenatal Diagnosis, 23 (11), 948–950. doi: 10.1002/pd.714

ONCOLOGIC OUTCOMES OF RADICAL PROSTATECTOMY AND PROGNOSTIC STRATIFICATION IN PATIENTS WITH CLINICALLY LOCALLY ADVANCED PROSTATE CANCER

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Abstract

Oncologic outcomes of radical prostatectomy in 106 patients with clinically locally advanced prostate cancer were demonstrated. The mean follow-up was 50.6 (12–129) months. 5-year recurrence-free survival was 47.7 %, 5-year cancer-specific and overall survival – 85.8 %. Patients were devided into three different risk groups: low risk patients had PSA level <20 ng/ml, biopsy Gleason score ≤6 and absence of the seminal vesicle invasion of cancer; intermediate risk was noted when the patient had only one of poor prognostic factors (PSA ≥20 ng/ml or biopsy Gleason score ≥7 or presence of cancer invasion to the seminal vesicle) and high risk patients had 2 or 3 poor prognostic factors. For patients of low, intermediate and high risk the biochemical reccurence rates were 14.3 %, 37.1 % and 70.2 %, respectively (p=0.002). The patients of intermediate and high risk had clinically significant higher risk of biochemical reccurence than those of low risk with odds ratio 3.0 and 8.5, respectively. Such grouping may help in guiding the individualized treatment for these patients.

Keywords: locally-advanced prostate cancer, prognostic stratification.

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1. Introduction

Locally advanced prostate cancer (PCa) is defined as a tumor that has extended beyond the prostatic capsule, including invasion of the periprostatic fat, bladder neck or seminal vesicles, but without regional or distant metastases. Nearly 20–25 % of cases present as locally advanced disease [1, 2]. Last years the incidence of PCa in locally advanced stage significantly decreased, primarily due to the early diagnosis improvement through the use of prostate-specific antigen (PSA) and needle biopsy. In 2013 in Ukraine, the percentage of locally advanced disease in the prostate cancer incidence was 23.1 % compared with 31.1 % in 2003 [3, 4].

The management of locally advanced PCa is one of the most compelling contemporary challenges. In the absence of randomized clinical trials comparing the effectiveness of radical prostatectomy (RPE), radiotherapy (RT), androgen deprivation therapy (ADT), or combination of these methods, it is difficult to determine the optimal treatment strategy for these patients. RPE with an extended pelvic lymphadenectomy is a proper treatment option of patient with locally advanced PCa accepted by international guidelines [5]. RPE benefits are to achieve the maximal tumor reduction and following pathological examination that allows to select patients who need adjuvant treatment. Prospective studies in this area allow only overall treatment strategies of this group of patients [6, 7].

Most of the studies devoted to the evaluation of oncological outcomes of RPE, RT or multimodality treatment of patients with locally advanced PCa face the challenge of heterogeneity within this group [8, 9]. When the most of these patients have the benefits of treatment, some patients die, despite the chosen option. Thus, it is necessary to review the current classification system and develop optimal stratification of locally advanced PCa.

2. Aim of research

To present the oncologic outcomes of RPE in patients with clinically locally advanced PCa and create a model of its prognostic stratification using combinations of accepted risk factors.

3. Material and methods

We identified and treated with RPE 106 patients with clinically locally advanced PCa (stage $cT_3N_0M_0$ according to the 2010 TNM system) between August 2002 and June 2015 at State Institution 'Institute of Urology of National Academy of Medical Sciences of Ukraine'.

Prostate biopsies were performed under transrectal ultrasound (TRUS) guidance, and pretreatment PSA was measured before digital rectal examination (DRE) or TRUS. A minimum of six biopsy cores was taken for each patient included in the study. All patients underwent a bone scan and a magnetic resonance imaging scan or pelvic computed tomography. Patients were excluded if they were found to have radiographic evidence of regional or distant metastatic disease.

Clinical stage was assigned according to the TNM system of 7th edition (2010) [10]. Clinical stage cT3a was determined in cases of tumor invasion beyond the prostate capsule without invasion of the seminal vesicles, cT3b – in cases of MRI or CT signs of tumor invasion in the seminal vesicles, cT4 – in case of tumor invasion in the external sphincter. **Table 1** presents the baseline characteristics of studying patients.

Out of all 106 patients, 31 (29.2 %) underwent laparoscopic RPE and 75 (70.8 %) underwent radical retropubic prostatectomy both with extended bilateral pelvic lymph node dissection. The RPE specimens including prostate, seminal vesicles, and bilateral pelvic lymph nodes were examined microscopically after routine preparation. The prostate was inked, weighted, and cut at 5-mm intervals. A positive surgical margin was defined as the presence of cancer cells extending into the inked surface of the prostate. A positive lymph node was defined as the presence of tumoral glands in at least one of the pelvic lymph nodes.

Follow-up included DRE, serum PSA measurement. Bone scan, MRI or CT were performed by indications. The serum PSA level was typically measured at 4 weeks and quarterly during the initial 2 years after surgery, semi-annually for an additional 3 years, and annually thereafter. Biochemical recurrence (BCR) was defined as evaluation of total PSA by >0.2 ng/ml. Biochemical recurrence free survival (BRFS) referred to time from RPE to biochemical reccurence constatation.

PCa-specific survival (PCSS) referred to time from RPE to death attributed to PCa or disease-related complications. Adjuvant therapy was defined as treatment received ≤90 days of RP, and was given at the discretion of the treating physician, while salvage therapy was defined as treatment received >90 days after RPE, and triggered by PSA recurrence or clinical progression.

The Kaplan-Meier method was used to estimate time-to-event outcomes and the log-rank method was used to compare survival. Cox proportional hazard regression was used to identify prognostic factors, which were employed in a stepwise selection approach. The assumption of proportional hazards was confirmed for each of the input variables. All P values are two-sided, and a level of 0.05 was considered statistically significant.

Table 1
Characteristics of the study population

Characteristic	Result
Mean age (range), years	62.2±0.6 (40–74)
Time of follow-up, months	55.7±3.2 (12–129)
Mean PSA (range), ng/ml	29.4±1.3 (2.5–150)
PSA<10 ng/ml, n (%)	8 (7.5)
PSA =10–20 ng/ml, n (%)	31 (29.2)
PSA >20 ng/ml, n (%)	67 (63.2)
Mean biopsy Gleason score	6.7 (5–9)
Gleason score 2–6, n (%)	49 (46.2)
Gleason score 7, n (%)	36 (34.0)
Gleason score 8–10, n (%)	21 (19.8)
Stage cT_{3a}, n (%)	52 (49.1 %)
Stage cT_{3b}, n (%)	55 (51.9 %)
Stage cT_{4}, n (%)	1 (0.9 %)

4. Results

Mean follow-up after RPE was 55.7±3.2 months, and 45 (42.5 %) patients had follow-up beyond 5 years. During the follow-up 55 (51.9 %) patients experienced biochemical recurrence, 18 died, with 16 dying of PCa. **Fig. 1** displays the BRFS and **Fig. 2** – PCSS for the entire cohort of clinically locally advanced PCa patients.

In univariable analysis the most important predictor of biochemical recurrence was clinical signs of tumor invasion in the seminal vesicles (hazard ratio (HR): 6.5; 95 % confidence interval

(CI), 2.8−13.3) followed by biopsy Gleason score ≥7 (HR: 1.7; 95 % CI, 0.8−3.6) and PSA ≥20 ng/ml (HR: 2.0; 95 % CI, 0.9−4.5).

On the basis of the three main clinical risk factors were established model of prognostic stratification of clinically locally advanced PCa into three subgroups: low, intermediate and high risk.

Low risk patients had PSA level <20 ng/ml, biopsy Gleason score ≤6 and absence of the seminal vesicle invasion of cancer (14 patients). Intermediate risk was noted when the patient had only one of poor prognostic factors (PSA ≥20 ng/ml or biopsy Gleason scor e≥7 or presence of cancer invasion to the seminal vesicle, 35 patients) and high risk patients had 2 or 3 poor prognostic factors (57 patients).

Oncological outcomes and pathomorphological features of tumors were significantly different in all three subgroups. For patients of low, intermediate and high risk the biochemical reccurence rates were 14.3 %, 37.1 % and 70.2 %, respectively (p=0.002) (**Fig. 3**), and the risk of its development in patients with intermediate risk grew 3.0, high − in 8.5 times.

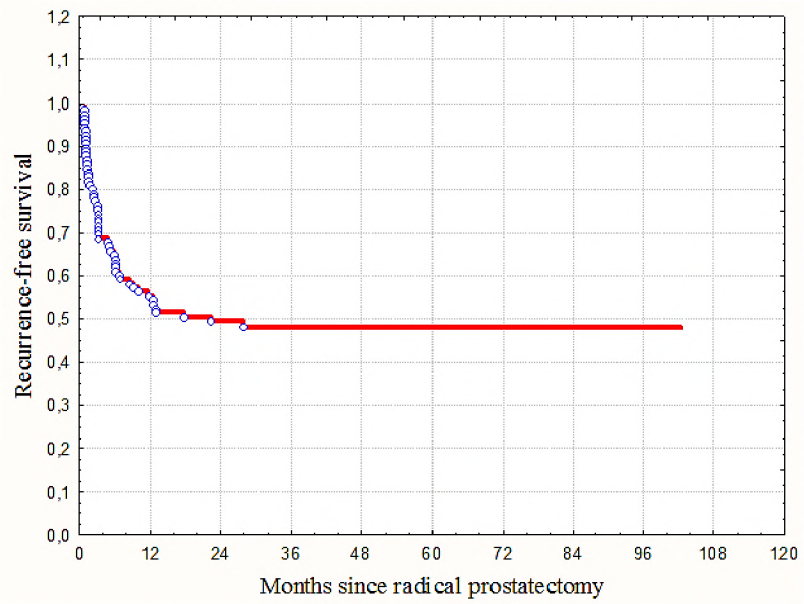

Fig. 1. Biochemical recurrence-free survival for the entire cohort of clinically locally advanced PCa patients

Proposed model demonstrated that most patients in low risk group were treated with RPE alone (adjuvant RT received 14.3 % of patients, adjuvant ADT − 26.8 %, and biochemical recurrence had only 2 of 14 patients (14.3 %)). In addition, 35.7 % of patients had pathologically organ-confined prostate cancer that occurred clinical overstaging of the disease.

On the other hand, a large number of high risk patients had poor pathomorphological characteristics of tumor. Positive surgical margin identified in 49.1 % of cases, perineural invasion − in 56.1 %, regional lymph nodes metastases − in 29.8 %. Most of patients in high risk group require multimodal treatment (adjuvant RT carried 40.4 % of patients, adjuvant ADT − 59.6 %) and had biochemical recurrence (40 of 57 patients, 70.2 %) (**Table 2**).

Obviously, the high-risk group includes patients with aggressive disease, regardless of the chosen treatment strategy. These patients should be in focus of the researchers of new treatment approaches of PCa.

The ambiguous place of intermediate risk in determining of optimal treatment option. Given the fact that 62.9 % of patients had no biochemical recurrence during the follow-up, adjuvant RT carried only 22.9 %, adjuvant ADT − 34.3 % of patients, and the frequency of poor prognostic features was lower than in the high-risk group, this group of patients can be offered RPE as a first-line method of treatment. Feasibility of adjuvant therapy should be decided after determining the pathological tumor characteristics.

Table 2
Pre- and postoperative patient characteristics related to prognostic subgroups

Characteristics	Risk group			p
	Low, n=14	Intermediate, n=35	High, n=57	
Mean age (range), years	64.4±1.6	61.8±1.0	61.9±0.8	0.351
Mean PSA level (range), ng/ml	13.0±1.1	23.8±1.9	36.9±3.6	0.0002
Mean Pathologic Gleason score	6.3	6.6	7.7	
Pathologic Gleason score ≤6, n (%)	9 (64.3)	18 (51.4)	5 (8.8)	0.0001
Pathologic Gleason score 7, n (%)	3 (21.4)	13 (37.1)	31 (54.4)	
Pathologic Gleason score ≥8, n (%)	2 (14.3)	4 (11.4)	21 (36.8)	
Pathologic stage				
pT_2, n (%)	5 (35.7)	11 (31.4)	4 (7.0)	
pT_{3a}, n (%)	4 (28.6)	15 (42.9)	9 (15.8)	0.0001
$pT_{3в}$, n (%)	4 (28.6)	8 (22.9)	37 (64.9)	
pT_4, n (%)	1 (7.1)	1 (2.9)	7 (12.3)	
Lymph node methastasis, n (%)	0	4 (11.4)	17 (29.8)	0.014
Perineural invasion, n (%)	5 (35.7)	15 (42.8)	32 (56.1)	0.262
Positive surgical margin, n (%)	1 (7.1)	8 (22.9)	28 (49.1)	0.002
Adjuvant RT, n (%)	1 (7.1)	8 (22.9)	23 (40.4)	0.027
Adjuvant ADT, n (%)	4 (28.6)	12 (34.3)	34 (59.6)	0.020
Salvage RT, n (%)	0	4 (11.4)	4 (7.0)	0.383
Salvage ADT, n (%)	2 (14.3)	5 (14.3)	9 (15.8)	0.977
Biochemal recurrence rate, n (%)	2 (14.3)	13 (37.1)	40 (70.2)	0.0001
Cancer specific deaths rate, n (%)	1 (7.1)	4 (11.4)	11 (19.3)	0.02

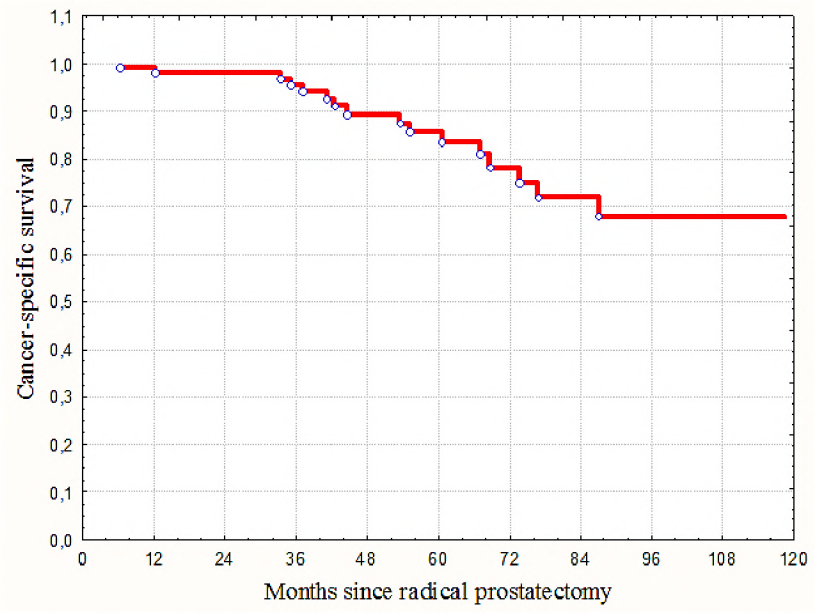

Fig. 2. Cancer-specific survival for the entire cohort of clinically locally advanced PCa patients

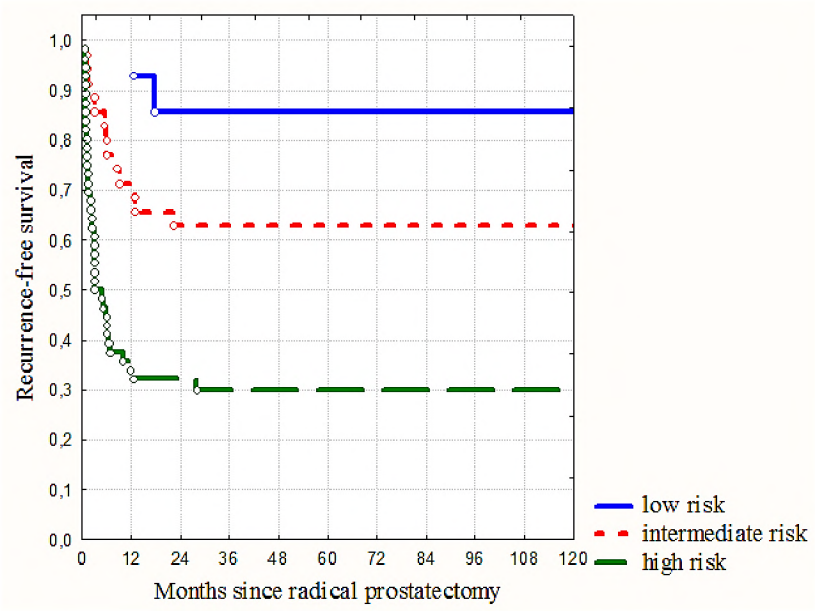

Fig. 3. Biochemical recurrence-free survival for the model of prognostic stratification of clinically locally advanced PCa with three prognostic subgroups

5. Discussion

Despite the clinical stage migration that has occurred with the advent of PSA screening, some patients continue to present with clinically locally advanced PCa [11]. The optimal treatment for this category of men remains controversial and is a matter of debate [12, 13].

The data on surgical management of locally advanced PCa has not been investigated or systematically reviewed and no large randomized controlled trial is available to show its superiority. Comparison of RPE with other treatment options for locally advanced PCa is questionable due to patients heterogenity and inherent selection bias of good prognosis patients in favor of surgery [8, 9, 14].

A few studies have shown promising results of RPE for locally advanced PCa [15, 16]. Xylinas et al. have shown oncologic outcomes in patients with T3 stage of PCa in few series of RPE. This meta-analysis has demonstrated 5-years BCRF, CSS and overall survival at 45−62 %,

84−98 % and 84−91 %, respectively [17]. Oncological outcomes of our study are similar to those reported in the literature series for clinically locally advanced PCa.

At diagnosis, PCa is usually classified into major risk categories based on TNM clinical stage, biopsy Gleason score and PSA level. It is generally assumed that patients with locally advanced PCa are at an elevated risk of experiencing biochemical recurrence, metastatic progression, and death from PCa [8, 18−20]. Our proposed model of prognostic stratification for patients with clinically locally advanced PCa was designed for use in clinical practice and comprises three prognostic subgroups: a low, intermediate and high risk. BCR rates and histopathologic features at RP were significantly different between the low, intermediate and high risk subgroups.

Also, proposed model demonstrates that many patients of low risk were treated with surgery alone and experienced exceptionally good 5-yr BRFS (85.7 %) and PCSS (92.8 %). Conversely, most individuals in the high risk subgroup necessitated a multimodal treatment (adjuvant RT: 40.4 %; adjuvant ADT: 59.6 %). Despite this much more intense treatment, 5-yr BRFS was significantly worse (29.8 %). Clearly, the subgroup of high risk patients includes men with aggressive disease despite more intense treatment. Ideally, these patients should be in target when studying new combined treatment approaches.

6. Conclusions

1. Patients with clinically locally advanced prostate cancer have higher risk of biochemical failure after radical prostatectomy but demonstrate good cancer-specific and overall survival.

2. The proposed stratification of locally advanced prostate cancer into three prognostic groups of low, intermediate and high risk is easy in use by urologists and researchers for selecting the optimal treatment strategy.

3. The patients of intermediate and high risk had clinically significant higher risk of biochemical reccurence than those of low risk with odds ratio 3.0 and 8.5, respectively.

4. The most of low risk patients can be treated with radical prostatectomy alone.

5. The most of patients in high risk has an aggressive disease, need for multimodality treatment and should be in focus of the researchers of new treatment approaches of prostate cancer.

References

[1] Gnanapragasam, V. J., Mason, M. D., Shaw, G. L., Neal, D. E. (2011). The role of surgery in high-risk localised prostate cancer. BJU International, 109 (5), 648–658. doi: 10.1111/j.1464-410x.2011.10596.x

[2] Van den Ouden, D., Schroder, F. H. (2000). Management of locally advanced prostate cancer. World Journal of Urology, 18 (3), 194–203. doi: 10.1007/s003459900102

[3] Fedorenko, Z. P., Goulak, L. O., Gorokh, Y. L. et. al. (2004). Cancer in Ukraine, 2002–2003. Bulletin of national cancer registry of Ukraine. Kyiv-2004, 43.

[4] Fedorenko, Z. P., Goulak, L. O., Gorokh, Y. L. et. al. (2015). Cancer in Ukraine, 2013–2014. Bulletin of national cancer registry of Ukraine. Kyiv-2015, 48–49.

[5] NCCN guidelines on prostate cancer, version 1. (2016). National Comprehensive Cancer Network Website. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

[6] Wiegel, T., Bottke, D., Steiner, U., Siegmann, A., Golz, R., Storkel, S. et. al. (2009). Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: ARO 96-02/AUO AP 09/95. Journal of Clinical Oncology, 27 (18), 2924–2930. doi: 10.1200/jco.2008.18.9563

[7] Dorff, T. B., Flaig, T. W., Tangen, C. M., Hussain, M. H. A., Swanson, G. P., Wood, D. P. et. al. (2011). Adjuvant Androgen Deprivation for High-Risk Prostate Cancer After Radical Prostatectomy: SWOG S9921 Study. Journal of Clinical Oncology, 29 (15), 2040–2045. doi: 10.1200/jco.2010.32.2776

[8] Yossepowitch, O., Eggener, S. E., Serio, A. M., Carver, B. S., Bianco, F. J., Scardino, P. T., Eastham, J. A. (2008). Secondary Therapy, Metastatic Progression, and Cancer-Specific Mortality in Men with Clinically High-Risk Prostate Cancer Treated with Radical Prostatectomy. European Urology, 53 (5), 950–959. doi: 10.1016/j.eururo.2007.10.008

[9] Carver, B. S., Bianco, F. J., Scardino, P. T., Eastham, J. A. (2006). Long-Term Outcome Following Radical Prostatectomy in Men With Clinical Stage T3 Prostate Cancer. The Journal of Urology, 176 (2), 564–568. doi: 10.1016/j.juro.2006.03.093

[10] Sobin, L. H., Gospodarowicz, M. K., Wittekind, Ch. (2010). International Union against Cancer. 7th ed. 2009. Chichester; New Jersey: Wiley-Blackwell, 243–248.

[11] Ward, J. F., Slezak, J. M., Blute, M. L., Bergstralh, E. J., Zincke, H. (2005). Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU International, 95 (6), 751–756. doi: 10.1111/j.1464-410x.2005.05394.x

[12] Carver, B. S., Bianco, F. J., Scardino, P. T., Eastham, J. A. (2006). Long-Term Outcome Following Radical Prostatectomy in Men With Clinical Stage T3 Prostate Cancer. The Journal of Urology, 176 (2), 564–568. doi: 10.1016/j.juro.2006.03.093

[13] Hakenberg, O. W., Frohner, M., Wirth, M. P. (2006). Treatment of Locally Advanced Prostate Cancer – The Case for Radical Prostatectomy. Urologia Internationalis, 77 (3), 193–199. doi: 10.1159/000094808

[14] Van Poppel, H., Joniau, S., Haustermans, K. (2007). Surgery alone for advanced prostate cancer? European Journal of Cancer Supplements, 5 (5), 157–169. doi: 10.1016/s1359-6349(07)70036-8

[15] Van Poppel, H., Goethuys, H., Callewaert, P., Vanuytsel, L., Van de Voorde, W., Baert, L. (2000). Radical Prostatectomy Can Provide a Cure For Well–Selected Clinical Stage T3 Prostate Cancer. European Urology, 38 (4), 372–379. doi: 10.1159/000020311

[16] Gontero, P., Marchioro, G., Pisani, R., Zaramella, S., Sogni, F., Kocjancic, E. et. al. (2007). Is Radical Prostatectomy Feasible in All Cases of Locally Advanced Non-Bone Metastatic Prostate Cancer? Results of a Single-Institution Study. European Urology, 51 (4), 922–930. doi: 10.1016/j.eururo.2006.08.050

[17] Xylinas, E., Dache, A., Roupret, M. (2010). Is radical prostatectomy a viable therapeutic option in clinically locally advanced (cT3) prostate cancer? BJU International, 106 (11), 1596–1600. doi: 10.1111/j.1464-410x.2010.09630.x

[18] D'Amico, A. V., Whittington, R., Malkowicz, S. B., Schultz, D., Blank, K., Broderick, G. A. et. al. (1998). Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. JAMA, 280 (11), 969–974. doi: 10.1001/jama.280.11.969

[19] Yossepowitch, O., Eggener, S. E., Bianco, F. J., Carver, B. S., Serio, A., Scardino, P. T., Eastham, J. A. (2007). Radical Prostatectomy for Clinically Localized, High Risk Prostate Cancer: Critical Analysis of Risk Assessment Methods. The Journal of Urology, 178 (2), 493–499. doi: 10.1016/j.juro.2007.03.105

[20] D'Amico, A. V., Moul, J., Carroll, P. R., Sun, L., Lubeck, D., Chen, M.-H. (2003). Cancer-Specific Mortality After Surgery or Radiation for Patients With Clinically Localized Prostate Cancer Managed During the Prostate-Specific Antigen Era. Journal of Clinical Oncology, 21 (11), 2163–2172. doi: 10.1200/jco.2003.01.075

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PREVALENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN PATIENTS WITH CORONARY HEART DISEASE AND ARTERIAL HYPERTENSION

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Abstract

The prevalence of chronic obstructive pulmonary disease among patients with cardio-vascular diseases is higher than in general population. At the same time the one of problems of internal medicine is a timely diagnostics of chronic obstructive pulmonary disease.

The aim of the work was the study of prevalence of chronic obstructive pulmonary disease among patients with cardio-vascular diseases, especially arterial hypertension and coronary heart disease.

Materials and methods. The retrospective analysis of statistical cards of patients, who were on stationary treatment at therapeutic departments, was carried out to estimate the prevalence of combination of chronic obstructive pulmonary disease with arterial hypertension. The target examination of 136 patients was realized for revelation of chronic obstructive pulmonary disease. All patients were interrogated by the original modified questionnaire of assessment of short breath by medical research council (mMRC), test for assessment of chronic obstructive pulmonary disease (CAT) and underwent spirography with bronchodilatation test.

Results. It was established, that 10,2 % of patients had the combination of chronic obstructive pulmonary disease with arterial hypertension. Among persons, who were on treatment as to the stable coronary heart disease and had not obstructive disease of respiratory organs in anamnesis, in 26,4 % the chronic obstructive pulmonary disease was diagnosed for the first time.

Keywords: chronic obstructive pulmonary disease, comorbid pathology, arterial hypertension, coronary heart disease, diagnostics.

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1. Introduction

The disease of respiratory organs and the ones of cardio-vascular system are often destined for co-existence. They often start at the same age, have common proved risk factors, series of similar pathophysiological mechanisms, namely: chronic hypoxia, rheological changes of blood and so on. It must be noted that essential ageing of the planet population resulted in increase of the number of persons, who have chronic diseases of respiratory organs, including chronic obstructive pulmonary disease and cardio-vascular diseases, first of all, arterial hypertension and coronary heart disease [1–3].

The prevalence of chronic obstructive pulmonary disease in the world among men and women is 9,3 % and 7,3 %, among smokers – 26,2 and 23,7 %, respectively [4, 5]. The meta-analysis of series of randomized studies established that the prevalence of chronic obstructive pulmonary disease in the world and Europe is on average 7,2 %, that is near four million and hundred people suffer from this disease, in city dwellers the prevalence of chronic obstructive pulmonary disease reaches 10,2 %, among men – 9,8 % and women – 5,6 % respectively, among patients, older than 40 years – 10 %, older than 65 years – 14,2 %, among smokers – 15,4 %, among persons, who never smoked – 4,3 %, among persons, who left smoking – 10,7 % [4, 6, 7].

The important factor that conditions the urgency of problem of chronic obstructive pulmonary disease is the high cost of this pathology for health protection system and society in whole.

According to the data of Global Initiative for Chronic Obstructive Lung Disease (GOLD), in European countries the annual direct expenditures for chronic obstructive pulmonary disease reach 38,6 billion dollars and indirect ones exceed 17 billion dollars [4].

At the same time the tendency to growth of the number of patients with cardio-vascular diseases, especially, arterial hypertension that is the one of main causes of morbidity and invalidism of population as a result of its prevalence, is observed in the world. Arterial hypertension is registered with frequency 15–20 % among adult population of the world and 30–60 % among patients of elder age group [8, 9]. Arterial hypertension is an important risk factor of development of complication in cardio-vascular system, injury of target organs that determines morbidity and early invalidism of patients [10, 11].

In Ukraine there are almost 12 million persons with arterial hypertension and only 14 % of them control the level of arterial pressure (AP) [12].

The scientists and doctors throughout the world deal with the problem of combination of chronic obstructive pulmonary disease and cardio-vascular system diseases. Thus, the ten-year retrospective analysis of the medical cards of stationary patients revealed that in 51,7 % of patients with chronic obstructive pulmonary disease was diagnosed the diseases of cardio-vascular system, most frequent among them were coronary heart disease – in 28,9 % , heart failure – in 19,6 %, rhythm disorder – in 12,6 % [1, 13, 14]. The frequency of concomitant cardio-vascular disorders increased with age and had the close connection with sex, there was observed the increase of the number of men with combination of chronic obstructive pulmonary disease and coronary heart disease. At combined clinical course of chronic obstructive pulmonary disease and concomitant CVD the frequency of hospitalization increased because of any diseases during the year [6, 15].

Some scientists consider chronic obstructive pulmonary disease as an independent risk factor of cardio-vascular complications [16]. Among patients with chronic obstructive pulmonary disease the prevalence of heart failure is 2 times more, stable angina 2,5 times more, peripheral vessels diseases 2,4 more, stroke 1,5 times more comparing with general population [17, 18]. So the problem of diagnostic of chronic obstructive pulmonary disease in patients with arterial hypertension and coronary heart disease is today urgent and rather difficult that determines the topicality of our studies.

2. Aim of research

Estimation of the prevalence of chronic obstructive pulmonary disease among patients with coronary heart disease and arterial hypertension, who visited health protection institutions for medical help.

3. Materials and methods

The study was carried out in three stages. At the first stage the retrospective analysis of 15 134 statistical medical cards of patients, who were on stationary treatment at therapeutic departments of the clinical hospital № 1 of Vinnytsia city during the period 2007–2009 were studied.

The other stage of the work was carried out in 2016 year. There was carried out the target diagnostics of chronic obstructive pulmonary disease of persons, who were on treatment at cardiologic department in 2016 for stable coronary heart disease and had not obstructive diseases of respiratory organs in anamnesis. The group of examination included 136 patients, mean age (61,6±1,02) years, men – 109 (80,1 %), women – 27 (19,9 %). The diagnosis of coronary heart disease, verified by the results of coronography was in 78 (57,3 %) patients, by anamnesis data as to Q-myocardium infarction in 105 (77,2 %) patients, surgical interventions as myocardium revascularization in anamnesis were observed in 57 (41,9 %)patients, including stenting of coronary arteries – 42 (30,8 %) patients, aortacoronary bypass – 15 (11 %) patients. Smoking was indicated by 79 (58 %) patients, smoking index among smokers (24,5±2,9) packet/years. The complicated professional anamnesis was in 33 (24,2 %) patients (**Table 1**).

Table 1
Characteristic of examined persons

Parameter (n=136)	Results
Number of patients	136
Mean age, years	61,6±1,02
Men, abs., (%)	109 (80,1 %)
Women, abs., (%)	27 (19,9 %)
Post-infarction cardiosclerosis, abs., (%)	105 (77,9 %)
Stable exertional angina, II functional class, abs., (%)	48 (35,3 %)
Stable exertional angina, III functional class, abs., (%)	85 (62,5 %)
Coronography, abs., (%)	78 (57,3 %)
Stenting of coronary arteries, abs., (%)	42 (30,8 %)
ACS, abs., (%)	15 (11 %)
Hypertonic disease, abs., (%)	116 (87,2 %)
Heart failure, I functional class, abs., (%)	5 (3,6 %)
Heart failure, II functional class, abs., (%)	103 (75,7 %)
Heart failure, III functional class, abs., (%)	25 (18,3 %)
Diabetes mellitus, abs., (%)	20 (14,7 %)
Obesity, abs., (%)	55 (40,4 %)
Smoking, abs., (%)	79 (58 %)
Complicated professional anamnesis, abs., (%)	33 (24,2 %)
Complicated hereditary anamnesis as to chronic obstructive pulmonary disease, abs., (%)	5 (3,7 %)
Complicated hereditary anamnesis as to coronary heart disease, abs., (%)	26 (19,1 %)

All patients, included in the study at the second stage of the work (n=136), were interrogated by original questionnaire, created on the base of GOLD 2015 recommendations for diagnostics of chronic obstructive pulmonary disease [4] (**Table 2**).

Table 2
Questionnaire for diagnostics of chronic obstructive pulmonary disease

Question questionnaire	Positive response	Negative response
Do you have permanent cough several times a day?	Yes	No
Do you cough up sputum every day?	Yes	No
Do you have short breath more often than your coevals?	Yes	No
Your age is more than 40 years?	Yes	No
Do you smoke or smoked in past?	Yes	No

The patients also underwent computer spirography with bronchodilatation test using 400 mcg of salbutamol (MasterScope ST) and interrogation by modified questionnaire of short breath assessment of medical research council (mMRC) and test of chronic obstructive pulmonary

disease (CAT) for determination of clinical group of chronic obstructive pulmonary disease, regulated by the order by HPM of Ukraine № 555 of 27.05.2013 and GOLD recommendations.

Statistical processing of the data was carried out using the package of statistical programs STATISTICA10.0 and MicrosoftExel. The reliability of difference of values was calculated by non-parametric method by χ^2 Pearson's criterion, U-test by Mann-Whitney and Student t-criterion at comparison of mean values.

4. Results of research

According to the results of the first retrospective stage of the work, it was established, that in period 2007–2009 at therapeutic departments of the hospital were treated 15134 patients, (8775 men (57,9 %) and 6359 women (42,1 %)). Among all patients 1538 patients with chronic obstructive pulmonary disease 10,2 % had concomitant arterial hypertension. Among men the prevalence of combination of chronic obstructive pulmonary disease with arterial hypertension was diagnosed in 880 patients (10,02 %), among women – in 658 (10,4 %).

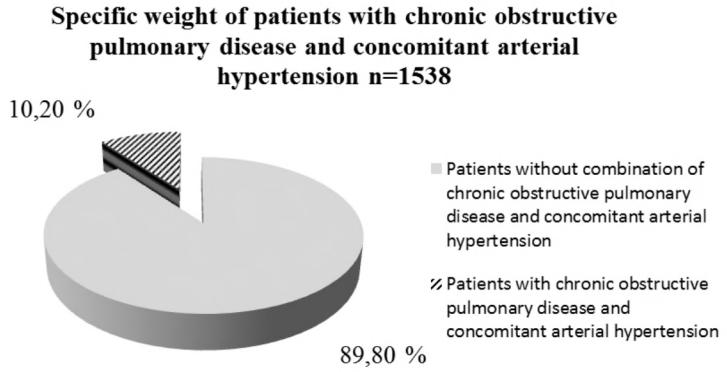

Fig. 1. Part of patients, treated at therapeutic departments of MCH № 1 during the period 2007–2009, and had combination of chronic obstructive pulmonary disease and concomitant arterial hypertension

The stable tendency to growth of the number of patients with combined pathology is observed annually. The growth of part of patients with polymorbid pathology has progressive character. Thus, in 2007 it was 8,17 %, in 2008 – 10,9 %, in 2009 – 12,42 % (**Fig. 2**).

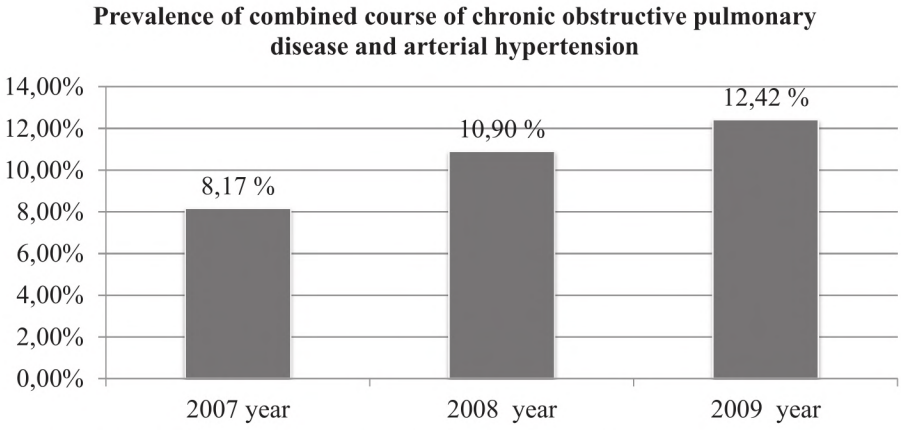

Fig. 2. Prevalence of combination of chronic obstructive pulmonary disease and cardio-vascular diseases at therapeutic departments of municipal hospital

There is observed certain tendency as to distribution of chronic obstructive pulmonary disease and arterial hypertension in different sex groups. Especially, in 2007 the prevalence of patients

with such combination was more among women than among men. Whereas in 2008 and 2009 men prevailed, that has a tendency to growth.

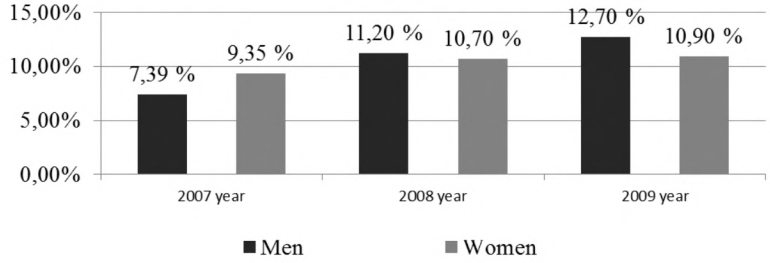

Fig. 3. Frequency of combination of chronic obstructive pulmonary disease and arterial hypertension at therapeutic departments of municipal hospital among men and women during the period 2007–2009

Most patients with comorbid pathology were hospitalized at pulmonological department, especially 1051 (68,3 %) persons, whereas at cardiologic one were 326 patients (21,2 %) and at therapeutic one – 161 persons (10,5 %).

According to the results of second stage of questionnaire work, it was established, that the positive answers to the questions of the questionnaire were given by all 136 patients with stable coronary heart disease. Among the interrogated patients 3 (2,2 %) gave the positive answer to only 1 question, 50 (36,7 %) persons – to 2 questions, 61 (44,9 %) – to 3 questions, 17 (12,5 %) patients – o 4 questions and 5 (3,7 %) persons – to all 5 questions of the questionnaire, respectively. It must be noted that 80 (58,8 %) interrogated persons gave the positive answer to 3 and more questions, so they have clinical symptoms, typical for combination of chronic obstructive pulmonary disease.

All patients underwent spirometry with bronchodilitation test. According to its results, combination of chronic obstructive pulmonary disease was diagnosed in 36 (26,4 %) patients with stable coronary heart disease, mean age (62±1,9) years (**Fig. 4**).

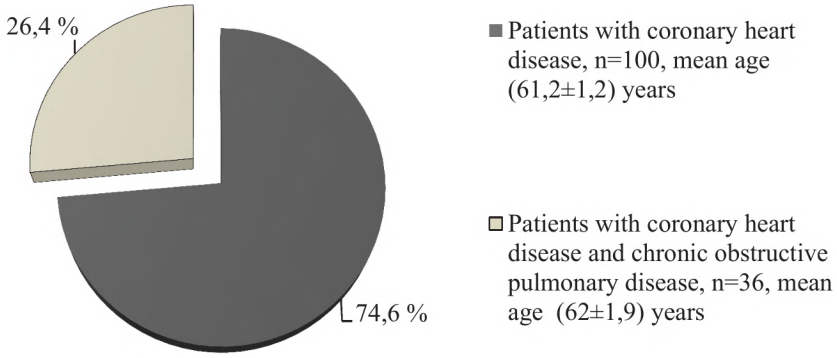

Fig. 4. Frequency of revelation of chronic obstructive pulmonary disease among patients with stable coronary heart disease, n=136

We analyzed two groups of patients, I included 36 persons with coronary heart disease with concomitant chronic obstructive pulmonary disease and II included 100 persons with coronary heart disease without diagnosed chronic obstructive pulmonary disease. Although the patients of both groups were of the same age, there is observed the tendency to most frequent manifestation of chronic obstructive pulmonary disease among men (91,7 % and 76 % respectively, p=0,07), who had more severe functional class of angina (69,4 % and 61 %, p=0,12), reliably more often after aortocoronary bypass (22,2 % and 7 %, p=0,04) and had heart failure of III functional class (30,6 % and 14 %, p=0,03). The diagnosis of heart failure of III functional class in patients of this category can be explained by underestimation of the symptoms of chronic obstructive pulmonary disease,

because short breath was assessed by doctors as a sign of heart failure. Among patients of I group comparing with two group was observed the tendency to more frequency of other concomitant diseases, namely hypertonic disease (88,9 % and 84 % respectively, p=0,22), diabetes mellitus (25 % and 11 %, p=0,06),obesity (47,2 % and 38 %, p=0,08) (**Table 3**).

Table 3

Characteristic of patients with stable coronary heart disease and concomitant chronic obstructive pulmonary disease and patients with stable coronary heart disease without concomitant chronic obstructive pulmonary disease

Characteristic	I group patients with stable coronary heart disease and concomitant chronic obstructive pulmonary disease, n=36	II group patients with stable coronary heart disease n=100
Mean age, years	62±1,9	61,2±1,2
Men, abs., (%)	33 (91,7 %)	76 (76 %)
Women, abs., (%)	3 (8,3 %)	21 (21 %)
Post-infarction cardiosclerosis, abs., (%)	26 (72,2 %)	79 (79 %)
Stable exertional angina, II functional class, abs., (%)	11 (30,5 %)	37 (37 %)
Stable exertional angina, III functional class, abs., (%)	25 (69,4 %)*	60 (60 %)*
Coronography, abs., (%)	17 (47,2 %)	61 (61 %)
Stenting of coronary arteries, abs., (%)	8 (22,2 %)	34 (34 %)
ACS, abs., (%)	8 (22,2 %)*	7 (7 %)*
Hypertonic disease, abs., (%)	32 (88,9 %)	84 (84 %)
Heart failure, I functional class, abs., (%)	0	5 (5 %)
Heart failure, II functional class, abs., (%)	25 (69,4 %)	78 (78 %)
Heart failure, III functional class, abs., (%)	11 (30,6 %)	14 (14 %)
Diabetes mellitus, abs., (%)	9 (25 %)	11 (11 %)
Obesity, abs., (%)	17 (47,2 %)	38 (38 %)
Smoking, abs., (%)	27 (75 %)	51 (51 %)

*Note: * – difference between groups is reliable, p<0,05, calculation was carried out using Pearson χ^2 criterion*

Patients with coronary heart disease and firstly diagnosed chronic obstructive pulmonary disease were distributed by the clinical groups of chronic obstructive pulmonary disease. Among 36 patients with stable coronary heart disease and chronic obstructive pulmonary disease 9 (25 %) patients were included in the group A, that is the patients with metasymptom course and low risk of complications, 17 (47,2 %) patients - in group B that is the patients with many symptoms of chronic obstructive pulmonary disease and low risk of complications, 2 (5,6 %) patients – in group C, who have little number of symptoms and high risk of complications, 8 (22,2 %) patients formed D group, they had many clinical symptoms of chronic obstructive pulmonary disease and high risk of complications.

5. Discussion of results

The analysis revealed the essential layer of patients, who had combination of chronic obstructive pulmonary disease and stable coronary heart disease and arterial hypertension. Such comorbidity is noted by the scientists of different countries. It can be explained by the series of factors, namely: essential ageing of population, spreading of risk factors, influence of professional and everyday factors [12, 14, 19]. The same factors play the essential role in formation of cardio-vascular diseases. At the same time it must be noted that the concrete data as to the prevalence of chronic

obstructive pulmonary disease in patients with cardio-vascular diseases are absent. Thus, the prevalence of arterial hypertension in persons with chronic obstructive pulmonary disease varies from 16 to 75 % according to the data of different scientists [17, 19].

The complications of diagnostics of these combined diseases appear as a result of late resort to medical help, little number of symptoms at early stages of disease. It must be also noted that patients' complaints are often considered by doctors as manifestations of other diseases, for example, heart failure but not of chronic obstructive pulmonary disease.

Despite the stereotype literary data about the prevalence of men among patients with combined clinical course, we established the tendency to the growth of women number with cardio-vascular pathology at the background of chronic obstructive pulmonary disease. Especially, the prevalence of combined course among men and women in 2007 was 7,39 % and 9,35 % respectively, in 2008 – 11,2 % and 10,7 % respectively, in 2009 – 12,7 % and 10,9 % respectively [11].

The special complications take place in diagnostics of chronic obstructive pulmonary disease in patients with stable coronary heart disease, because in this group of patients the use of functional methods of examination, especially spirography with broncholithus is limited. This very point of view is shared by doctors of general practice. It is argued by the data about the influence of broncholithus on heart rate, electrolytic changes. So, it is important to elaborate the simple available screening methods that allow to select patients for further functional examination with high reliability degree [11, 20–22]. This very aim is set in our work.

It is worth attention, that in all patients, who gave 4 or 5 positive answers to the questions of the questionnaire, chronic obstructive pulmonary disease was diagnosed after examination of the function of external breath that testifies to the possibility of using this questionnaire to select patients with coronary heart disease for spirometry that is expedient for timely diagnostics of chronic obstructive pulmonary disease. Undoubtedly, our research is today limited only by retrospective analysis and examination of the small group of patients with stable coronary heart disease. Our further observations and studies will allow widen the data as to the features of course of chronic obstructive pulmonary disease in different categories of patients.

6. Conclusions

1. Thus, there is a numerous general therapeutic group of patients with diagnosed combination of chronic obstructive pulmonary disease with arterial hypertension, namely – 10,2 %.

2. According to the data of retrospective analysis, there is observed the progressive growth of the number of persons with combined pathology, namely chronic obstructive pulmonary disease with arterial hypertension from 2007 to 2009 year from 8,17 % to 12,42 %. These patients visit a pulmonologist most often.

3. Chronic obstructive pulmonary disease was diagnosed in 36 (26,4 %) patients after the target diagnostics among ones with stable coronary heart disease, who had not obstructive diseases of respiratory organs in anamnesis.

4. It was noted, that chronic obstructive pulmonary disease of A and B groups that had the low level of unfavorable events development was diagnosed in 26 (72,2 %) patients and in 10 (27,8 %) – C and D groups, associated with the high risk of unfavorable changes and complications.

5. In the group of patients with previously non-diagnosed chronic obstructive pulmonary disease prevail men (91,7 %), smokers (75 %) with other concomitant diseases, especially arterial hypertension (88,9 %), obesity (47,2 %), diabetes mellitus (25 %).

References

[1] Westerik, J. A. M., Metting, E. I., van Boven, J. F. M., Tiersma, W., Kocks, J. W. H., Schermer, T. R. (2017). Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. Respiratory Research, 18 (1), 31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5294875 doi: 10.1186/s12931-017-0512-2

[2] Gupta, M. (2011). Pattern of Comorbidities in hospitalized elderly patient of chronicobsrtuctive pulmonary disease. Journal of The Indian Academy of Geriatrics, 7, 6–11.

[3] Ye, C., Younus, A., Malik, R., Roberson, L., Shaharyar, S., Veledar, E. et. al. (2016). Subclinical cardiovascular disease in patients with chronic obstructive pulmonary disease: a systematic review. QJM, 18, hcw135. doi: 10.1093/qjmed/hcw135

[4] Global Initiative for Chronic Obstructive Lung Disease. Available at: http://www.goldcopd.com

[5] Yin, P., Wang, H., Vos, T., Li, Y., Liu, S., Liu, Y. et. al. (2016). A Subnational Analysis of Mortality and Prevalence of COPD in China From 1990 to 2013. Chest, 150 (6), 1269–1280. doi: 10.1016/j.chest.2016.08.1474

[6] Mooe, T., Stenfors, N. (2014). The Prevalence of COPD in Individuals with Acute Coronary Syndrome: A Spirometry-Based Screening Study. COPD: Journal of Chronic Obstructive Pulmonary Disease, 12 (4), 453–461. doi: 10.3109/15412555.2014.974742

[7] Geldmacher, H., Biller, H., Herbst, A., Urbanski, K., Allison, M., Buist, A. et. al. (2008). The prevalence of chronic obstructive pulmonary disease (COPD) in Germany. DMW – Deutsche Medizinische Wochenschrift, 133 (50), 2609–2614. doi: 10.1055/s-0028-1105858

[8] Roversi, S., Roversi, P., Spadafora, G., Rossi, R., Fabbri, L. M. (2013). Coronary artery disease concomitant with chronic obstructive pulmonary disease. European Journal of Clinical Investigation, 44 (1), 93–102. doi: 10.1111/eci.12181

[9] Cordero, A., Bertomeu-Martinez, V., Mazon, P., Facila, L., Bertomeu-Gonzalez, V., Cosin, J. et. al. (2011). Factors Associated With Uncontrolled Hypertension in Patients With and Without Cardiovascular Disease. Revista Espanola de Cardiologia, 64 (7), 587–593. doi: 10.1016/j.rec.2011.03.007

[10] Miliutina, O. V., Chicherina, E. N. (2009). Rol khronicheskogo vospalitelnogo protsessa v progressirovanii aterosklerosa u patsientov s khronicheskoi obstruktivnoi bolezniu legkikh v sochetanii s arterialnoi hipertoniei. Pulmonolohiya, 3, 43–46.

[11] Rabahi, M., Alves Pereira, S., Rodrigues Junior, J. L., Rezende, A. P., Castro da Costa, A., Sousa Correa, K., Conde, M. B. (2015). Prevalence of chronic obstructive pulmonary disease among patients with systemic arterial hypertension without respiratory symptoms. International Journal of Chronic Obstructive Pulmonary Disease, 10 (1), 1525–1529. doi: 10.2147/copd.s85588

[12] Pertseva, T. O., Gashynova, K. Yu., Yefimova, N. O. (2010). Pokaznyky funktsii endotelijyu y cholovikiv, shcho paliat, iz khronichnym obstruktyvnym zakhvoriuvannam legen [Indices of endotheial functions in males, smokers with chronic obstructive pulmonary disease]. Medychni perspectyvy, 3, 36–40.

[13] Bolton, C. E., Quint, J. K., Dransfield, M. T. (2016). Cardiovascular disease in COPD: time to quash a silent killer. The Lancet Respiratory Medicine, 4 (9), 687–689. doi: 10.1016/s2213-2600(16)30243-0

[14] Griffo, R., Spanevello, A., Temporelli, P. L., Faggiano, P., Carone, M., Magni, G. et. al. (2017). Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: Evidence from SUSPIRIUM, a multicentre Italian survey. European Journal of Preventive Cardiology, 24 (6), 567–576. doi: 10.1177/2047487316687425

[15] Shilov, A. (2009). Osobennosti lechenija IBS v sochetanii s KHOBL. Lechashchij vrach, 7, 44–48.

[16] Andell, P., Koul, S., Martinsson, A., Sundstrom, J., Jernberg, T., Smith, J. G. et. al. (2014). Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. Open Heart, 1 (1), e000002. Available at: www.ncbi.nlm.nih.gov/pmc/articles/PMC4189340/ doi: 10.1136/openhrt-2013-000002

[17] VandeBorne, P., Wauters, A., Parati, G. (2012). Air pollution and hypertention. European Society of Hypertention Scientific Newsletter: Updateon Hypertention Management, 12, 51–52.

[18] Hua, C., Dong-Mei, M., Zhi-Min, W., Jian-Fang, C., Yi, L., Ai-Min, L., Fan, L. (2012). Prevalence of cardiovascular disease in subjects hospitalized due to chronic obstructive pulmonary disease in Beijing from 2000 to 2010. Journal of Geriatric Cardiology, 9 (1), 5–10. doi: 10.3724/sp.j.1263.2012.00005

[19] Karoli, N. A., Borodkin, A. V., Rebrov, A. P. (2015). Certain problems of diagnostics of chronic cardiac insufficiency in patients with chronic obstructive pulmonary disease. Klin Med (Mosk), 93 (5), 50–56.

[20] Karrasch, S., Bruske, I., Smith, M. P., Thorand, B., Huth, C., Ladwig, K.-H. et. al. (2016). What is the impact of different spirometric criteria on the prevalence of spirometrically defined COPD and its comorbidities? Results from the population-based KORA study. International Journal of Chronic Obstructive Pulmonary Disease, 11, 1881–1894. doi: 10.2147/copd.s104529

[21] Kaplan, A., Thomas, M. (2017). Screening for COPD: the gap between logic and evidence. European Respiratory Review, 26 (143), 160113. Available at: http://err.ersjournals.com/content/26/143/160113.long doi: 10.1183/16000617.0113-2016

[22] Ostrovskyi, M. M. (2011). Bronkhoobstruktyvnui syndrom: aktualni pytannia diagnostyky ta likuvannja. Ukraynskyy Pulmonolohichnyi zhurnal, 2, 14–16.

PSYCHOHYGIENIC ASPECTS OF TRAINING OF DISABLED ADOLESCENTS WITH PATHOLOGY OF THE VISION

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Abstract

The objective of this article is to undertake a literature review to familiarize ourselves with the knowledge base; to summarize information about some psycho-hygienic aspects of teaching and visually impaired adolescents, including features of communication, learning environment, psycho-emotional stress in specialized educational institutions, as well as individual psychological characteristics of personality, emotional and volitional state of visually impaired and general patterns of physiological and psychological characteristics and health of adolescents with vision pathology. To examine the system of security measures in order to optimize the learning environment for the promotion of mental health of the studied contingent and the nature and impact of the learning environment on functional status and health of adolescents with vision pathology. To investigate the impact of current patterns of complex sanitary and regime-organizational factors of training on functional status and health of adolescents with vision pathology. A thorough literature review helps to lay the foundation for a study, and can inspires new research ideas.

Keywords: psychohygiene, the blind and visually impaired, psychoprophylaxis, education, visual disturbances, prenosological state.

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1. Introduction

According to the World Health Organization (WHO) today there are 40 million blind people in the world, 1.5 million of them − are children. As for Ukraine, 40 thousand people are suffering from true blindness and visually impaired people are five times more. And this number is increasing every year.

It is known that one of the most common causes of disability is blindness. Today, a variety of visual disturbances are extremely common worldwide. In recent years there was a tendency to growth of severe and disabling diseases that lead to loss of vision. Apart the causes, heredity, injury, complications at birth, infectious diseases, and common to all human diseases − environmental degradation, canned excess, etc. Important role played the tendency of civilization progress: the dominant role of vision, as a means of receiving and processing information. Each year, the flow of information increases, the visual system adapts to such loads much slower.

Throughout last few years the national programs to preserve and improve the health of the most vulnerable groups, namely children and adolescents with disabilities, namely "Children of Ukraine" (1996), the Concept of Health Development of Ukraine (2000), the Interdepartmental complex program "Health of the nation" (2002−2011) were adopted and actively implemented, and nationwide program "Health 2020: Ukrainian dimension" is currently developed.

2. Aim of research

The objective of this article is to summarize information about some psycho-hygienic aspects of teaching the blind and visually impaired adolescents.

3. Psychohygienic aspects of learning for the blind and visually impaired

One of the most urgent problems of today is the health of children and adolescents as well as reduction of the number of healthy children. Increasing proportion of children with chronic diseases and people with disabilities greatly reduces the potential for development of the country. In the last decade throughout the world, including Ukraine, a lot of attention is paid to the occurrence of child disability. The growth of the total number of children with disabilities and a high level of primary disability among the child population define the necessity of the state level measures for

the correction of social policy for children with disabilities, the basic directions of that should be the prevention of disability, medical and pedagogical rehabilitation of children with disabilities, social adaptation, conducting primary preventive measures aimed at improving the stability of mental health, resilience of the psyche of children – defenseless against the influence of various environmental factors that would entail the prevention of severe secondary somatic and neuropsychiatric consequences already at the initial stage of their manifestations without severe socially significant violations [1].

According to the current classification blind persons are those, whose visual acuity is in the range from 0 % to 0,04 %. Thus, contingent includes people fully devoid of vision (totally blind) and with residual vision (visual acuity from light perception to 0,04 %). Children with visual acuity from 0,05 % to 0,2 % are in the category of visually impaired, and may have to work with the help of sight under certain hygienic requirements [2].

One of the priorities of the existence and development of the prosperous state is to take care about getting high-quality and high-grade education by all the representatives of the younger generation, as stipulated in the Law of Ukraine "Higher Education", which is associated with creation of the necessary conditions for quality education of persons with disabilities including the blind and visually impaired. Totally blind children use touch and hearing to obtain educational information. Blind children with residual vision also obtain core training information through the sense of touch and hearing because such a profound defeat of vision use for a long time entails a negative impact on its further development. However, in the process of training and education residual vision is not ignored because it gives children more information about the environment. For a student with a visual disturbance it is important even before the start of classes to learn the movement and orientation in classrooms. It is necessary to maintain a constant placement of furniture and equipment in the classroom, and inform the visually impaired student about any changes in the room. Foreign methodologists prefer horseshoe seating arrangement of students when the teacher is in an open part of the "horseshoe" for easy access of all trainees to teacher. It is necessary to allow the student to sit where he better sees the board, but not separately from other students. In the room it is necessary to provide modifiable lighting conditions; because students may have different visual impairment, requirements to lighting are different for each student, in particular, adjustable lighting in different parts of the class is required to create different lighting conditions to meet the individual needs of students; local illumination, where it necessary; natural lighting and blinds to limit natural light and glare if necessary. The classroom should be with perfect acoustics, because the sound is very important for a blind student. It is also necessary to minimize the extraneous sounds. Special coating of the walls and floor softens the sound and improves the learning environment, and conversely uncovered floor can create an echo and distort intonation [3].

Visually impaired and disabled − is a special case, since 80 % of the information people receive through the visual analyzer [4, 5]. With a sharp decrease of vision, it interferes with the normal ability to self-care, movement in space, and also severely limits the possibility of learning and social interaction.

For a clearer perception of the problems of children with disabilities two groups of factors should be highlighted: the objective, depending on surrounding reality and subjective, depending directly on the person that can lead to mental health problems.

The objective factors include: a negative public perception of the disabled; low levels of social support, protection and assistance to persons with disabilities; not well-appointed accommodation and public areas for use by people with disabilities; low level of social status.

Subjective factors include: life position, consisting in passive and not an effort to feel like a full member of society; psychological self-awareness, underestimation of their capabilities, hidden personal potential; lack of life objectives, settings; rejection by society (isolation, aggression); the desire to learn, to work, to live [6].

It is known that all training programs must be aimed at solving the triune task: training and strengthening of health of students with regard to special schools for pupils with eye pathology, the additional challenges are facing them because they need to focus on both medical-social and psycho-hygiene aspects of training.

For medical and social rehabilitation of students, adolescents with disabilities, with the pathology of vision it is necessary to develop a methodological program for the study of the functional state and health of adolescents, disabled due to ophthalmic pathology, which includes adequate, well proven currently researching methods, as well as the adaptation of special methods to study the functionality of people with ophthalmologic diseases.

According to many scientists, one of the most important factors influencing the functional state of the organism, its adaptation possibilities, level of health (both mental and physical), is a psychoemotional stress. Depending on the causes and conditions conducive to appearance of stress, the different stressful situations which early detection and elimination of risk factors of their occurrence can prevent the development of pathological processes are available [7].

Overcoming of borderline conditions helps the applying of adaptogenic measures. They are aimed at training the organism functions contained in the reactions of individual adaptation practices and maintaining constitutional evolutionarily conditioned defense mechanisms. In the period of adaptation and a compensatory stress of different severity adaptogenic activities should be preserving, correcting, and at the stage of adaptation "collapse" − with reducing character. Measures for the correction should be based on the objectification of evaluation of the organism functional state at the level of prenosological − premorbid state, as a result of mismatch between the organism capabilities and environmental requirements, which provokes predictors of pathological process [8].

One of the main tasks of the modern psychohygiene is providing mental health of individuals and population as a whole. Not less important task is psychohygiene − implementation of the measures of primary psychoprophylaxis, aimed at improving the mental health for resistance to the influence of various environmental hazards [7]. A subject of direct study of psychohygiene is presented by such common mental conditions such as personality accentuation, which under certain conditions can be transformed into the corresponding psychopathy - condition of the morbid character; various types of deviant behavior that bring personal and social danger; a wide range of borderline mental states that accompany the situation and risk periods and has neurotic character [8].

Prenosological states arise from dysfunction of the adaptive systems, which are currently intended to ensure stable functioning of the organism, and therefore the preclinical diagnosis is based on the definition of qualitative and quantitative indicators of the adaptation process, measured, and (or) calculated as a result of prophylactic examinations. The use of monitoring observation of the state health of students in special educational institutions for blind and visually impaired in the complex of hygienic diagnostic measures resolves the significantly extend of our views on the formation of prenosological states among students and accordingly propose a system of preventive measures for the correction of the functional state of the organism [8, 10–12].

Based on the direct and reverse incremental regression analysis, the statistical models that allow to predict the degree of probability of prenosological shifts in mental health, are developed, taking into account the characteristics of the living and social conditions, the mode of the day and training adaptation, characteristics of the psycho-physiological functions development of the body and the personality traits [13, 14].

4. Result

Introduction into the research activity of the borderline states involves the creation of well-structured system of diagnostic and corrective measures, enabling consistently meet the challenges of population health assessment, sanitary and preclinical diagnosing and hygienic correction of the functional state of the organism, whose ultimate goal is the preservation of the individual, population and public health [15].

However, it is necessary to emphasize that the current system of primary prevention is actually deprived of an extremely important element, which consists of objectification of evaluation of the functional state of the organism at prenosological state level in circumstances, where non-compliance, non-conformity of the organism capacity to environmental requirements and social conditions generate prerequisites for the formation of the pathological process [16, 17].

Basic hygienic measures in special schools for children with pathology of the organ of vision are the prenosological hygienic diagnostics of the health state of students. It involves a detailed study of the whole complex of educational and domestic factors in connection with their targeted influence on child and adolescent organism. In addition, the development of methods for the detection and measurement of individual psychological characteristics of personality is needed [18]. The objective of these programs is to establish qualitative and quantitative characteristics of external influence. During experimental work on studying the modes of learning for the blind and visually impaired in specialized educational institutions one of actual tasks is to establish a thin line that separates the normal reaction to external environmental impacts from pathological manifestations.

Thus, the basis of our research is a natural experiment that allows to develop the set of effective measures of psychohygienic correction of the functional state of students, as well as to justify scientifically prognostic criteria for assessing social adaptation of the studied contingent, using modern adapted techniques. The search criteria for assessing the level of health are important to make timely and adequate organizational, medical and social measures for the correction of premorbid states [19, 20].

5. Conclusions

Thus, the analysis of foreign and native literature on sociocultural rehabilitation of people with special needs, gives grounds to say that:

1. The sphere of social protection and support is developing pretty rapidly in almost all countries of the world, but I can't mention the lack of study of the combined effect of educational and household activities on the functional state and the state of mental health of the adolescents with disabilities of organ vision, which belong to the "group of risk" of prenosological deviations in neuro-psychic sphere.

2. Today the task of studying and managing the development of child personality with special needs with a view to its fulfillment in the world of sighted people should be clearly set at the top of the issue.

3. For the organization of competent pedagogical work we must take into account not only the age, but also the individual characteristics of children, due to their personal psycho-emotional qualities, as well as differentiated features associated with the diagnosis of eye diseases, the degree of visual impairment and their health.

References

[1] Faal, H., Gilbert, C. (2007). Convincing Governments to act: VISION 2020 and the Millennium Development Goals. Community Eye Health Journal, 20 (64), 62–64.

[2] Zhaboedov, G. D., Skrypnyk, R. L., Baran, T. V. (2011). Ophthalmology. Kyiv, 412.

[3] Methodology of Teaching a Foreign Language to the Blind. Project "LISTEN & TOUCH": A Basic English Course for the Visually Impaired. Socrates programme: Lingua-2.

[4] Zavyalova, A. V., Smirnova, V. M. (2009). Normal physiology. Moscow: "MEDpress-Inform", 631.

[5] Rosenberg, E. A., Sperazza, L. C. (2008). The visually impaired patient. Am Fam Physician, 77 (10), 1431–1436.

[6] McLeod, B. D., Southam-Gerow, M. A., Tully, C. B., Rodríguez, A., Smith, M. M. (2013). Making a Case for Treatment Integrity as a Psychosocial Treatment Quality Indicator for Youth Mental Health Care. Clinical Psychology: Science and Practice, 20 (1), 14–32. doi: 10.1111/cpsp.12020

[7] Biryukov, N. A. (2006). Healthcare technologies in educational institutions. Hygiene and sanitation, 1, 76–77.

[8] Lesovoy, V. N., Kapustnik, V. A., Korobchanskiy, V. A. (2013). Medicine of borderline conditions: theory and practice of prenosological diagnostics. Scientific journal of Health Ministry of Ukraine, 2 (3), 49.

[9] Psychohygiene: Ukrainian-Russian Dictionary (2008). Kharkiv: Contrast, 192.

[10] Korobchanskiy, V. A. (2005). Hygienic psychodiagnostics of prenosological states in adolescence and early adulthood. Guide for doctoral students, graduate students, applicants and physicians. Kharkiv: Contrast, 4–5.

[11] Korobchanskiy, V. A., Mikheev, V. V., Vasilchenko, I. O. (2007). Psychohygienic problems of prenosological diagnostics of adolescent's mental health problems. Bulletin of Hygiene and Epidemiology, 11 (2), 232–233.

[12] Korobchanskiy, V. A., Vytrischak, S. V. (2015). Hygienic prenosological psychodiagnostic: methodological basis and practical perspectives. Environment and Health, 4, 9–14.

[13] Bardov, V. G., Serheta, I. V. (2000). Hygienic basis of prediction the health of children and adolescents. Problems of medicine, 1-2, 41–46.

[14] Serheta, I. V., Bratkova, O. Y. (2007). Hygienic aspects of diagnostics and correction of changes in the emotional sphere of 15–17 years old adolescents. Bulletin of Hygiene and Epidemiology, 2, 234–237.

[15] Korobchanskiy, V. O., Reznichenko, O. G., Veremiyenko, O. V. (2015). Hygienic assessment and optimization of the functional state of students in higher education institutions through the introduction of the medicine of extreme conditions principles. Experimental and clinical medicine, 3 (68), 157.

[16] Serheta, I. V. (2013). Prenosological changes in mental state, modern psychohygienic approaches to interpretation, diagnosis and evaluation. Scientific Journal of Health of Ukraine, 3 (4), 36.

[17] Cone, J. D. (1997). Issues in functional analysis in behavioral assessment. Behaviour Research and Therapy, 35 (3), 259–275. doi: 10.1016/s0005-7967(96)00101-5

[18] Korobchanskiy, V. A. (2007). Psychohygiene: our understanding in 2007. Medical practice, 1, 108–115.

[19] Serheta, I. V. (1995). Hygienic aspects of rehabilitation of teenagers the marginal psychological disorders. Medical Rehabilitation, 4, 19–22.

[20] Korobchanskiy, V. A., Lantukh, A. P., Vitrischak, S. V., Brodetsky, Y. U. (2008). The phenomenon of marginality in the modern Ukrainian society: methodological, sociological and psycho-hygienic aspects. Lugansk: LugGMU, 312.