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PROSOPOGRAPHY OF KHARKIV MEDICAL INSTITUTE IN 1945–1991

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Abstract

The article aims to determine and consider the typical features of the key healthcare organizers in the post-war Soviet Kharkiv. The author created the collective portrait of 15 prominent physicians, scholars and administrators who got education or made a career at Kharkiv Medical Institute. In particular the origin, work path, professional achievements and civic activity were taken into account. As a result the author came to such conclusions: pre-war repressions and the WWII caused the gap of generations in the medical community despite preservation of the certain scientific schools; the relative separation of duties on public-administrative and scientific was noticeable among the healthcare organizers; engagement of women to the healthcare management became widespread; formation of the post-war generation of healthcare administrators was influenced by war outcomes, isolation of a medical science and education, ideological pressure, formal mandatory public activity and importance of informal party and professional ties for the career advancement. The preliminary set of personal qualities typical for the post-war generation of medical administrators was distinguished in comparison with qualities of their teachers – representatives of the last pre-Soviet generation. The prospects of the further studies were outlined such as study of informal vertical and horizontal relations at Kharkiv Medical Institute.

Keywords: *Kharkiv Medical Institute, post-war era, prosopography, Soviet healthcare.*

The main pillar of the Soviet regime throughout the entire period of its existence was the state and party bureaucracy, the *nomenklatura*. The intellectual and ideological degradation of the party elite became one of the factors for almost peaceful collapse of the USSR. Thus it's important to disclose cadre policies of Soviet times including a closed professional medical environment.

There is a reason to use prosopography for study of social institutions. The article's goal is to trace evolution of professional and personal characteristics of the post-war physicians with the change of generations, character of connections within the community, understand place of the outstanding healthcare organizers in the context of historical period. Creation of the collective portrait of the organizer of Kharkiv healthcare will allow determining typical features of the post-war generation of medical workers and factors of their formation.

Such research should start in a certain organization taking into account the specificity of labor relations in a collective. The study involved assessment of biographies of 15 scientific and medical workers of Kharkiv Medical Institute.

The research focused on bright personalities of healthcare, heads of Kharkiv Medical Institute departments who built their career after the World War II: Yevhen Dubenko, Volodymyr Chernenko, Olena Hrechanina, Valentyn Hryschenko, Mykola Koreniev, Oleksiy Korzh, Lyubov Mala, Mykola Pylypenko, Oleksandr Shalimov, Volodymyr Shapoval, Yuri Shul'ha, Vadym Topuzov, Anatoly Tsyhanenko, Volodymyr Zajtsev, Boris Zadorozhnyj. Born before the World War II, mostly in 1920s, they came from families of peasants (4), officials (4), intelligentsia (3), workers (1). 10 of them were Ukrainians by nationality. 10 became Doctors of Sciences and professors in age 35–43. 12 studied at Kharkiv Medical Institute after the World War II and were students of physicians who graduated

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during the tsarist times: pathophysiologist Danylo Al'pern, pediatrician Volodymyr Belousov, forensic expert Mykola Bokarius, obstetrician and gynecologist Ivan Hryschenko, microbiologist Vasyl Derkach, orthopedist and traumatologist Mykola Novachenko, anatomist Rafail Synel'nykov, epidemiologist Mykhailo Solovjov, biochemist Aron Utevs'kyj [1, p. 214, 222, 258]. All of them were pioneers of new treatment methods (reanimation, vascular surgery and combustiology, nephrology, transplantation of bones and joints, stage treatment of cardiovascular diseases, in vitro fertilization) and founders of clinics and research institutes of the new type (Laboratory of clinical genetics, Institutes of urgent surgery, cryobiology and cryomedicine, therapy, the largest in the USSR urological center). All those personalities were heads of scientific societies and were editors of scientific journals, all were awarded the high state awards.

Continuity of scientific schools during the considered period partly was saved: in a traumatology and orthopedics that is the line Mykhailo Sytenko (1885–1940) – Mykola Novachenko (1898–1966) – Oleksiy Korzh (1924–2010); in a teraphy – Petro Shatilov (1869–1921) – Viktor Kohan-Yasniy (1889–1958) – Yuri Shul'ha (1920–2002); in a microbiology – Damian Hryn'ov (1880–1934) – Vasyl Derkach (1894–1973) – Anatoly Tsyhanenko (1929–2012) [2, p. 171].

After the World War II the bright group of the pre-Soviet generation of doctors had continued to work: pathophysiologist Danylo Al'pern (1891–1968), founder of Kharkiv Clinical Infectious Disease Hospital Ilya Braude (1890–1958), founder of the Ukrainian psychoneurological institute Oleksandr Hejmanovych (1882–1958), the inventor of insulin in the USSR Viktor Kohan-Yasniy (1889–1958), anthropologist Lev Nikolaiev (1898–1954), the author of original way of pain relief during a childbirth Kostiantyn Platonov (1877–1969), the founder of pathophysiological school in the Soviet psychiatry Viktor Protopopov (1880–1957), the author of first Soviet "Atlas of human anatomy" Rafail Synel'nykov (1896–1981), the founder of Ukrainian stomatology Mojsej Fabrykant (1864–1951) and many other first-rate specialists. Those people trained youth in 1940–1960s. Except professional ties the generations continuity at Kharkiv Medical Institute was provided with the help of creative evenings which were organized by students for their teachers [1, p. 246].

Nevertheless, we can assume that due to social and political transformations in the first half of the 20th century the gap between generations of pre-revolutionary and Soviet intelligentsia occurred. That was noticed by the prominent cardiologist Mykola Amosov (1913–2002), older peer of Oleksandr Shalimov and Lyubov Mala, who was a student of the world-class surgeon Sergei Sergeevich Yudin (1891–1954). M. Amosov recalled: "Surgeons of my youth were not very intelligent anymore, aristocrats - those I did not find… Not like Yudin. English, French, music, theater, paintings" [3, p. 266]. Students of Mykola Bokarius characterized him in that way: "… he made an impression of the man from another time"; "…radiated intelligence and generosity" [1, p. 233, 236]. The student of Viktor Kohan-Yasniy (1889–1958) noticed: "… he was a profound and versatile educated person, marked by the real intelligence. He knew the classic literature brilliantly, wasn't stranger to literature creativity… Since gymnasium years he was passionate about theater… for several years he was a member of the artistic council of the Russian drama theater in Kharkiv… co-director-producer of the outstanding play "People in white coats" [ibid., p. 250]. One of the closest disciples of the prominent pediatrician Volodymyr Belousov (1895–1971) left such precise characteristic of him: "That was a man that first of all *served the Science, not himself*, because he was infinitely decent before the Science, the same as was descent before the people. "Everything what I have done in pediatrics, in science, in pedagogy – just a result of my desire to be a good physician" [4, p. 44].

Factors that influenced the formation of the post-war generations of healthcare managers were their social origin; difficult post-war years when most of them studied at the institute; specificity of the stuff recruiting when the preference was given to Komsomol activists and party members; spread of protectionism and "blat" (informal favors) [1, p. 269; 3, p. 258; 5].

The education interrupted by the war, poverty and ideological campaigns of the late-Stalinist period, isolation and politicization of medical science and education in the late 1940s – early 1950s required from that generation a great devotion, self-discipline but at the same time caused formation of a certain tough character and attitude to subordinates [1, p. 276; 6, p. 16]. The role of the official ideology in medical education is clarified by memoirs of the director of the Institute for medical radiology Mykola Pylypenko who wrote that obtaining mark "4" ("good") for exam in the History of CPSS led to

his not inclusion to the list of those who were appointed for scientific work [1, p. 258].

Unlike the graduates of the imperial universities, representatives of the post-war generation didn't have an opportunity to continue studying and doctor's practice abroad. In conditions of the technological backwardness of the Soviet healthcare that fact had a negative impact on formation of young physicians and restricted their culture and worldview in general. Only reliable doctors who made a solid career, earned reputation, occupied responsible offices and were allowed by party committees had access to trips abroad for professional development [5].

The Soviet surgeon and writer Vladimir Golyakhovsky who emigrated to the USA in the late 1970s noticed that "In fact the party itself had expanded the boundaries of protectionism – people started to be accepted to work and advanced only through the party affiliation, not by other criteria" [ibid.]. However, not all Kharkiv doctors agree with such statement, that's why it requires further consideration with a subsequent proof or refute. V. Golyakhovsky asserts that mentioned situation negatively impacted the qualitative composition of healthcare administrators. Also he paid attention that party provided line to prevent Jews from occupation of high administrative offices or getting scientific degrees. Indeed among the lead scientific and administrative workers of Kharkiv Medical Institute of the post-war generation almost there were no Jews [1, p. 275].

The separation of duties between party activists and offspring of the old professors' families can be illustrated by the biographies of two peers – Mykola Mykolayovych Bokarius (1899–1966) and Illarion Pylypovych Kononenko (1900–1972). The son of founder of the Ukrainian forensic medicine Mykola M. Bokarius started his scientific activity immediately after the graduation of the Kharkiv Medical Institute. In 1931 in age of 32 he became a professor of the Department of Forensic Examination KhMI being its head for the next 35 years [ibid., p. 27]. But the peak of his administrative career was the post of Institute's vice-rector. Born in a peasant family Illarion Kononenko during the studying actively participated in a public life of the Institute which he graduated 11 years later than M. Bokarius. Unlike him I. Kononenko headed Poltava and later Vinnitsa healthcare (1935–1938). He worked as a director of several medical institutes and in 1944–1946 even became the Soviet Ukraine narkom (minister) of healthcare [ibid., p. 96]. Herewith I. Kononenko managed to became the candidate of medical sciences only in 1946. Thus we can assume that healthcare management was primarily in hands of the Komsomol and party activists from below while for those who did not want to make an administrative career and wished to continue the family traditions were allocated a scientific sphere. Although it did not make them free from necessity to enter the Communist Party. Such mandatory formal practice became as destructive for science as for the party itself.

The new positive feature of the post-war era was wide entrance of women to the highest management of the medical institutions: the head of the laboratory of clinical genetics Olena Hrechanina, the director of the Theraphy Institute Lyubov Mala, dean of the pediatric faculty and vise-director of the KhMI Vera Matveeva, the head of city ophthalmologic clinical hospital Tamara Kovalenko, the director of the Scientific Research Institute for Children and Adolescents Health Care Oleksandra Kornilova, head of the department of psychiatry of the KhMI Nina Tatarenko, the head of Kharkiv Clinical Infectious Disease Hospital Tetiana Shaposhnykova [7, p. 203–204; 8, p. 54, 154, 156, 167, 169–170].

The activity of healthcare organizers on a creation of contemporary research and medical institutions in Kharkiv in 1970s–1980s fit into the global context of the in-depth specialization in health. That fact could be used as a background for research to reveal the mechanisms and limits of the individual initiative of administrators in the post-Stalinist USSR where the terrorist methods of influence had not acted or could not be applied at the same scale as in 1930s–1940s anymore. The problem question for the next studies could be formulated in this way - what had become a new incentive for creative activity of managers in healthcare and other spheres of life after J. Stalin and before M. Gorbachev when the Communist Party maintained its absolute power but had to provide more flexible politics?

The suggestions about set of personal qualities typical for the pre-Soviet and post-war generations of medical administrators requires the further confirmation. If first ones were characterized by delicacy, modesty, self-devotion, attention to the people, universal culture that went beyond the professional interests, self-demanding, voluntary civic activity, composure, so for representatives of the post-war generation were common strong will, authoritarian style of management, severity, diligence, persistence, formalized civic activity [1,

p. 273; 6, p. 13, 24]. Memoirs of colleagues and disciples about the pioneer in anesthesiology and intensive care medicine, surgeon Oleksandr Shalimov reveal such details: "Being the greatest master of surgical technique, the professor was intolerant to the slightest awkwardness of assistants not sparing strong words for their missteps" [9, p. 172].

The remark about famous academician and founder of the Therapy Institute Lyubov Mala made by one of her successful disciples looks crucial for the understanding post-war generation: "What was Lyubov Trofymovna guided by in her purposeful vigorous activity? I don't think that anyone knows for sure because she didn't like to expatiate on this delicate topic. I guess she was far from indifference about a career of the outstanding scholar, healthcare organizer, recognition that was well deserved… But the peculiarity is that personal interests of Lyubov Trofymovna always coincided with the public ones. Finally everything that she achieved by her diverse activities was done for the people and left to them. Including the Therapy Institute that she created and which is no wonder named after her" [6, p. 25–26].

The separate question worth of studying is a behavior style and patterns of the Soviet healthcare administrators and the extent to which those patterns encouraged subordinates to work effectively. The potentially useful would be a study of network of horizontal and vertical relations among workers of Kharkiv Medical Institute.

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SUBCLINICAL CARDIAC DAMAGE IN CARDIOPULMONARY POLYMORBIDITY (REVIEW) PART 1

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Abstract

Hypertension and chronic obstructive pulmonary disease are one of the frequent comorbid conditions in internal medicine and are subject to meaningful cooperation among physicians, cardiologists, and pulmonologists.

A combination of chronic obstructive pulmonary disease and hypertension presents certain diagnostic and therapeutic challenges. These conditions share common risk factors, similar clinical presentations and some common parts of pathogenesis. The problem of association between chronic obstructive pulmonary disease and hypertension may be currently discusses both as a simple combination of various clinical entities, and as chronic obstructive pulmonary disease resulting in development of factors contributing to hypertension. One way or another, either a simple combination, or a mutually aggravating syndrome, but we state there is a cardiorespiratory continuum where chronic obstructive pulmonary disease acts as a valid component of hypertension development, and vice versa. Thus, it seems to be relevant to study peculiarities of the structural and functional status of the cardiovascular system and microcirculation, systemic remodeling mechanisms, endothelial dysfunction and inflammation in presence of chronic obstructive pulmonary disease -associated hypertension. Problems of additional cardiovascular risk marker development, treatment efficiency assessment remain topical.

Use of electrocardiography and echocardiography with dopplerometry has been an important diagnostic principle of subclinical cardiovascular damage in presence of hypertension and chronic obstructive pulmonary disease comorbidity. Non-invasive imaging methods play a central part in diagnostics of subclinical target organ damage. Wide implementation thereof is based on high diagnostic accuracy, common availability, safety and relatively low price.

Keywords: *hypertension, chronic obstructive pulmonary disease, comorbidity, electrocardiography, echocardiography with dopplerometry.*

Hypertension (HT) is one of the most serious common chronic diseases in humans causing disability and significantly reducing life length by 15–20 years on average. According to the WHO, between 10% and 30% of adult population in developed countries have HT.

A deeper investigation into clinical complications of HT resulted in development of a cardiovascular risk concept. A sufficient body of statistical data based on numerous epidemiological studies was collected allowing saying that every studied factor contributes to development, course, progression and outcome of this cardiac pathology.

Experts from the European Society of Hypertension (ESH) and the European Society of Cardiologists (ESC) extensively study the issues of concern related to stratification of the cardiovascular risk, treatment approaches, develop promising areas for future research. The major conclusions are summarized in units. The first unit addresses the following issues of concern: evaluation of subclinical target organ

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damage for complete cardiovascular risk stratification; treatment approaches; treatment strategy; therapeutic approach in particular conditions; treatment of concomitant risk factors.

Of particular note is the concept of target organs damage - heart, vessels, kidneys – by HT with the rationale for analysis methodology of subclinical damage thereof for the purpose of quantifying the overall cardiovascular risk which is of particular importance for optimization when treatment initiation, intensity and goals are decided.

Chronic obstructive pulmonary disease (COPD) is defined as a condition characterized by partially irreversible airflow restriction which is constantly progressing and associated with inflammatory reaction of pulmonary tissue to irritation by various pathogenic agents and gases [1].

A prevailing verification component in COPD identification is bronchopulmonary manifestations; however, extrapulmonary signs of COPD have been increasingly discussed lately, because clinical studies prove that development of COPD extrapulmonary effects have an important clinical and prognostic significance and define COPD as a systemic condition.

Cardiovascular diseases are diagnosed in at least 50% of patients with chronic obstructive pulmonary disease (COPD), which significantly increases risk of cardiovascular disease development two- or threefold [2]. HT and COPD are one of the frequent comorbid conditions in the internal medicine and are subject to meaningful cooperation among physicians, cardiologists, and pulmonologists [3].

A combination of COPD and HT presents certain diagnostic and therapeutic challenges. These conditions share common risk factors, similar clinical presentations and some common parts of pathogenesis. The problem of association of COPD and HT may be currently discusses both as a simple combination of various clinical entities, and as COPD resulting in development of factors contributing to HT. One way or another, either a simple combination, or a mutually aggravating syndrome, but we state there is a cardiorespiratory continuum where COPD acts as a valid component of HT development, and vice versa.

Development of these conditions is underpinned by a complex of pathogenic mechanisms aiming target organs directly or indirectly - through damaging a vessel wall, developing endothelial dysfunction, and increasing arterial stiffness. Those factors include hypoxemia at rest or on exertion, smoking, oxidative stress, systemic inflammation. Mutual aggravation and progression in case of combination of bronchopulmonary conditions and cardiovascular pathology are based on similar parts of pathogenesis (pulmonary and cardiac microcirculation impairment, pulmonary hypertension) causing early development of cardiorespiratory complications [4, 5].

According to numerous researchers, COPD and HT are mainly associated through endothelial dysfunction and systemic inflammation.

Endothelial Dysfunction

Cardiovascular effects, including endothelial damage leading to endothelial dysfunction (ED), are considered to be among the potential systemic presentations of COPD. Endothelium of vascular intima fulfils barrier, secretory, hemostatic and vasotonic functions, plays an important part in vascular wall inflammation and remodeling processes. ED may be defined as an imbalance between relaxing and constricting factors, anti- and procoagulant mediators, growth factors and inhibitors thereof. COPD patients show early ED development in pulmonary and systemic circulations associated with changes in collagen-elastin exchange in vascular walls due to hypoxemia, exposure to cigarette smoke pollutants, hemodynamic and oxidative stress, systemic inflammation, and proteinase-proteinase inhibitor system imbalance.

The literature data suggest that ED development is currently one of the major factors of pulmonary hypertension (PH) pathogenesis associated with COPD. Pulmonary heart disease development with change of the right and, at certain stages, left compartments of heart may be considered COPD systemic presentation. The concept of endothelial regulatory role in PH pathogenesis is mainly based on findings from *in-vitro* animal tests or tests with human preparations, meanwhile there are only few *in-vivo* studies. ED role in PH pathogenesis was studied predominantly in patients with primary PH where vascular wall structural impairments are acknowledged as the basis for pathogenesis.

ED is one of the first presentations of COPD-associated vascular complications which are identified at early stages of the condition, aggravate increasing respiratory disturbance, hypoxemia and tissue hypoxia. The association between bronchial obstruction and bronchial inflammation accompanied by increase in neutrophil and macrophage counts in bronchoalveolar lavage fluid presenting as

decrease in FEV1 (forced expiratory volume), and systemic inflammatory response with endothelial damage was proven. ED has been an object of interest lately, since ED is associated with high cardiovascular risk. Therefore, it is feasible in COPD-associated HT treatment to prescribe antihypertensive drugs which should both lower blood pressure efficiently, and exert positive effect on endothelial function, reduce pulmonary hypertension, decrease severity of systemic inflammatory response having no negative impact on one's respiratory system [6].

Chronic Systemic Inflammation

Chronic systemic inflammation syndrome, which plays a predominant role in the pathogenic cascade both for HT, and for COPD, may be considered as another global association mechanism. Chronic systemic inflammation is a typical multi-syndrome pathological process developing in response to the systemic damage and characterized with total inflammatory responsiveness of endotheliocytes, plasma and cell blood factors, connective tissue, and, at terminal stages, forms pathological microcirculation disturbances in vital organs and tissues [7, 8].

In presence of COPD, even if clinically stable, subclinical systemic inflammation accompanied by significant effect of pro-inflammatory cytokines on skeletal muscle metabolism, specifically, on their regeneration, is often observed. Fabbri and Rabe suggest viewing COPD as a "chronic systemic inflammatory syndrome" [9-11].

Subclinical systemic inflammation is considered to potentially induce development of systemic presentations in the presence of COPD [12, 13].

Fabbri et al. proposed a new approach to diagnosis, severity assessment and management of COPD and its frequent concomitant conditions, which lies in identification of the *"chronic systemic inflammatory syndrome"* signs [14]. Patients with moderate and severe COPD both during its acute condition, and its steady course, were proven to show signs of systemic inflammation confirmed by increase in circulating cytokines (TNF α [tumor necrosis factor α], IL-6 [interleukin 6], and IL-8 [interleukin 8]), chemokines and proteins of acute phase [15].

COPD patients display impairment of vasoactive endothelial function, pro-inflammatory cytokine balance, and increase in circulating immune complex concentration even at an early stage of the condition. The developed systemic inflammation and endothelial dysfunction (ED) directly and indirectly contribute both to development of pulmonary hypertension and chronic pulmonary heart disease, and development of left ventricular failure; increase in plasma endothelin concentration associated with COPD may be viewed as one of the signs of ED presence. This biologically active substrate activates receptors on smooth muscle cells, induces steady vasoconstriction and proliferation of small vascular media, stimulates further activation of pro-inflammatory cytokine cascades, maintains persistence of the chronic inflammation, and enhances platelet adhesion and microthrombi formation [16].

Clinical studies suggest that COPD is accompanied by development of pulmonary hypertension in 30–50% of cases. Presence of pulmonary hypertension complicates prognosis and is one of the major factors which determine survival in COPD patients. It has been determined that life prognosis in COPD patients becomes unfavorable when pulmonary hypertension becomes stable and circulation deficiency develops. Two thirds of COPD patients die during the period between 15 months and 5 years after circulatory decompensation development which occupies the third place after hypertension and chronic coronary insufficiency among causes of death in the age group of over 50. Despite the fact that decompensated chronic cor pulmonale (CCP) causes death in 30–37% due to circulatory deficiency and in 12.6% of all cases – due to cardiovascular diseases, early diagnosis of CCP, its decompensation and development of effective treatment remain topical; finding solutions to these problems is inseparable from understanding CCP pathogenesis. An inflammatory response which is excessive in intensity and duration intensifies the endocrine system activity with enhanced release of hormones and neurotransmitters into blood, and cytokine regulation imbalance. It is no doubt that there is a correlation between the systemic inflammation and cardiovascular diseases [17]. Haplotypes associated with increase in C-reactive protein (CRP) concentration do not cause cardiovascular pathologies as such [18]. Thus, CRP is more likely to be a marker rather than a cause of such concomitant diseases. In presence of COPD, there is a direct association between a level of the systemic inflammatory response and artery rigidity [19].

The major mediators of the chronic systemic response include pro-inflammatory interleukins

(IL-1, 2, 6, 8, 9, 12, 18) [20], tumor necrosis factor (TNF?) [21], matrix metalloproteinases [22].

Biomarkers specific for COPD-associated inflammation may include desmosine isomers [23], leukotriene B4 [24], IL-8, neutrophil elastase and surfactant protein D [25].

Among HT pathogenic mechanisms in COPD patients, the major role is played by primary sympathoadrenal system (SAS) activation. Thus, COPD-associated HT pathogenesis involves a renal part which lays in hyperactivity of renin-angiotensin-aldosterone system (RAAS), enhancement of juxtaglomerular system activity, renin and angiotensin 2, with the renal mechanism of COPD-associated HT quickly becoming a predominant one. In presence of bronchial obstruction in combination with HT, high RAAS activity is observed as early as at the initial COPD stage and hyperactivity of its tissue components is reported. Enhanced RAAS activity may cause hypokalemia in COPD patients leading to progression of respiratory disturbance through diminution of breathing muscular strength [26].

Thus, it seems to be relevant to study the peculiarities of the structural and functional status of the cardiovascular system and microcirculation, systemic remodeling mechanisms, endothelial dysfunction and inflammation in presence of COPD-associated HT. Problems of additional cardiovascular risk marker development, treatment efficiency assessment remain topical.

Use of electrocardiography and echocardiography with dopplerometry has been an important diagnostic principle of subclinical cardiovascular damage in presence of HT and COPD comorbidity. Non-invasive imaging methods play a central part in diagnostics of subclinical target organ damage. Wide implementation thereof is based on high diagnostic accuracy, common availability, safety and relatively low price. EchoCG allows for fast evaluation of the heart size, valvular heart apparatus status, systolic and diastolic functions of ventricles.

Structural biomarkers of subclinical organ damage

Electrocardiography

Electrocardiography (ECG) still remains the most available and relevant method in various diagnostic algorithms. PAC-COPD Study – 2013 [27] results show presence of myocardial structural and functional pathology in 64% of chronic obstructive pulmonary disease (COPD) patients when they are referred to an in-patient department for the first time, with 27% of patients displaying left heart damage, and 48% displaying right heart damage.

ECG signs of Right Atrial Hypertrophy

Right atrial myocardial hypertrophy results in increase of its excitation vector, leading to increased amplitude and duration of the first portion of the P-wave, with virtually no changes in left atrial depolarization processes; in this regard, the right atrial excitation ends almost simultaneously with the left atrium. The sum of the right and the left atrial vectors results in a high sharpened P-wave, often referred to as P-pulmonale (*Fig. 1*).

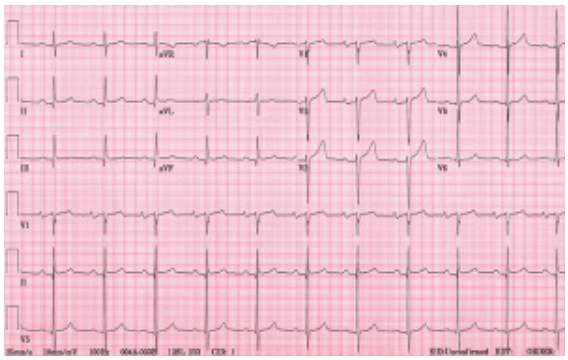

Fig. 1. Right Atrial Hypertrophy (P-pulmonale)

ECG findings show the following:

1. High (over 2.5-mm amplitude), sharpened, symmetrical P-wave with normal duration (0.1 second) in leads II, III, AVF.

2. P-wave electrical axis deviation to the right (PIII > PII > PI), with a somewhat smoothed P-wave in leads I and AVL.

3. In AVR: a deep, sharpened negative P-wave is recorded.

4. In chest leads – V1, V2 a high-amplitude (over 1.5-mm) sharpened or diphasic P-wave with predominant positive first phase (+/-). Depending on hypertrophy severity, similar changes may be recorded for the leads between V_1 and V_5; however, the P-wave amplitude in $V_{5–6}$ leads lowers.

5. In leads III, AVF and V1: activation time elongation for 0.04 seconds is recorded [28].

Right atrial myocardial hypertrophy may be additionally confirmed with the Macruz index calculation:

$$\frac{\text{P-wave (seconds)}}{\text{PQ segment (seconds)}}$$

In presence of the right atrial hypertrophy, it will be less than 1.1.

The amplitude criteria (P II>2 mm, P V_1>1 mm) displayed high P-pulmonale specificity: for men – 100%, for women – 94%; however, the performed analysis comparing these ECG criteria with echocardiography findings, namely, with the right atrial volume index recommended as a determinant for the right atrial size, showed

somewhat low sensitivity of these markers; P V_1>1 mm (66.%) and P II>2 mm (48%) showed the highest sensitivity without any gender differences [29]. Similar data were also displayed for structural and volumetric findings with cardiovascular magnetic resonance: ECG was 96 – 100% specific, but its sensitivity made up 17% [30].

ECG signs of Right Ventricular Hypertrophy

In presence of the right ventricular hypertrophy (RVH), sum excitation vector of the QRS complex shifts to the right and anteriorly resulting in the increased R-wave amplitude in right precordial leads. The more severe the RVMH is, the more the balance of cardiac ventricular vectors changes and the more the dominant effect of the left ventricular excitation vector reduces.

Electrocardiographic findings may include several presentations of RVH: the first one: predominance of the R-wave (in the QRS complex) in the right precordial leads, so-called R-type: such changes are specific for severe RVH and pressure overload; the second variant: ECG is comparable to the picture of the incomplete right bundle branch block and may be recorded in case of pressure overload, and the third variant: presence of deep S-waves in all chest leads at moderate RVH – S-type. The first and the second variants are often recorded in patients with chronic obstructive pulmonary diseases, the third variant is recorded for chronic non-obstructive pulmonary diseases.

Severe RVH, hypertrophied right half of the interventricular septum changes orientation of the initial sum excitation vector right to left; with further depolarization, two oppositely directed vectors interface: left and right ventricles – a sum vector is formed due to a hypertrophied right ventricle and is oriented toward it, i.e. left to right. In the context of delayed depolarization in the hypertrophied right ventricle, its repolarization processes start near endocardium, while in the left ventricle they start as usual from epicardium leading to change in normal direction of the sum repolarization vector, and it deviates to the left (*Fig. 2*).

Fig. 2. Right Ventricular Hypertrophy

ECG displays so-called R-type right ventricular hypertrophy:

1. High R-wave (more than 7 mm) in $V_{1–2}$ leads, with R $V_1 \geq$ S V_2
2. Deep S-wave (more than 7 mm) in $V_{5–6}$ lead
3. Decrease in amplitude R V_5, V_6 <5 mm
4. R/S ratio in V_6 leads α 1
5. R V_1 + S V_5 or R V_1 + S V_6> 10.5 mm (Sokolow index)
6. The QRS complex in the right precordial leads is graphically displayed as qR or R, less often as Rs, and in the left leads – as rs or RS; furthermore, the more severe the right ventricular myocardial hypertrophy is, the higher the R-wave in $V_{1–2}$ leads and the deeper the S-wave in $V_{5–6}$ leads are.
7. ST segment: a downsloping or upward-oriented curve depression is recorded in $V_{1–2}$ leads with $V_{5–6}$ elevation
8. The T-wave is negative, asymmetric in $V_{1–2}$ leads, and positive in $V_{5–6}$ leads.
9. The electrical cardiac axis (ECA) deviation to the right has an α angle ≥110°.

Moderate Right Ventricular Hypertrophy or S-Type

In the presence of this type, there is no severe interventricular septal hypertrophy and the sum excitation vector has a typical left-to-right orientation, ongoing depolarization processes in the right and left ventricles result in formation of the excitation vector oriented right to left; however, its size will be somewhat smaller than normal due to the dominant effect of the excitation vector of the hypertrophied right ventricle. Repolarization processes often have a typical course (*Fig. 3*).

In presence of this type of hypertrophy, ECG changes may be absent or may be displayed as insignificant changes in R- and S-wave amplitudes in chest leads and ratio thereof, namely, as

Fig. 3. Moderate Right Ventricular Hypertrophy or S-Type

somewhat increased R-wave amplitude in $V_{1–2}$ leads (up to 6 mm) with decrease in $V_{5–6}$ down to 3 mm [31], with decreased intensity of the S-wave depth in $V_{1–2}$ and increase thereof in $V_{5–6}$. The heart apex turning posteriorly displayed at ECG as deep S-waves in standard (S_I–S_{II}–S_{III}, with maximum in the second lead) and precordial leads with the rS complex graphical pattern and transitional zone shifting to the left, and ECA deviation to the right with the α angle ≥110° are recognized as typical criteria. The ST interval changes are insignificantly displayed or absent.

Right Ventricular Hypertrophy with Incomplete Right Bundle Branch Block

In this RVH type, initial depolarization processes have a typical course with formation of a left-to-right-oriented sum excitation vector; however, the right interventricular septal hypertrophy may result in the dominant influence of a vector of the left half being levelled out, leading to decreased sum vector amplitude. Similar changes are also observed in ventricles aggravated by the delayed depolarization course in the right ventricle which continues after the end of the left ventricular myocardial excitation leading to formation of a left-to-right-oriented vector. A hypertrophied right ventricle also affects repolarization processes shifting its sum vector to the left (*Fig. 4*).

Fig. 4. Right Ventricular Hypertrophy with Delayed Excitation and Incomplete Right Bundle Branch Block

ECG findings display the following:

1. The pattern of the complex is rsR' or rSR' (R' v1 > r v1) in V1 and qRS in V1 with its duration not more than 0.12 seconds.

2. Decrease in the R-wave amplitude in V_6 and the S-wave depth in V_1.

3. Increase in the S-wave depth and duration in V_{5-6}.

4. The right ventricular (RV) activation time in V_1 is increased up to 0.05 seconds.

5. The ECA deviation to the right has an α angle ≥110°.

6. ST segment: a downsloping or upward-oriented curve depression is recorded in $V_{1–2}$ leads with $V_{5–6}$ elevation.

7. The T-wave is negative, asymmetric in $V_{1–2}$ leads, and positive in $V_{5–6}$ leads.

Other amplitude criteria of RVH include presence of a delayed R-wave with its amplitude at least 4 mm in the AVR lead, with development of the QR complex or rSR' pattern; the Lewis index (R I + S III)–(S I + R III) is less than 15 mm; the Butler-Leggett index (maximum R V1,2+ maximum S I, V_6 – S V_1) is more than 6 mm.

RVH identification criteria show high specificity and sensibility both during ECG findings assessment and its comparison with the cardiac magnetic resonance imaging findings; the most sensitive (89%) and specific (93%) LVH criteria included ECA deviation to the right with the α angle >90°, presence of a high-amplitude R-wave > 5 mm in V1, R/S> 1 and the QRS complex pattern in V1 as rsr' or rsR' [32]; however, other criteria, such as the Butler-Leggett index, turned out to be a highly specific (100%), but insensitive (74%) RVMH marker [33].

ECG signs of Left Atrial Hypertrophy

Depolarization processes in a hypertrophied left atrium (LAH) are more prolonged leading to increase in sum excitation vector shifting it to the left and somewhat downward; ECG findings display a two-humped wide P-wave (p-mitrale) – the first portion of the wave reflects an unchanged right atrial excitation vector, and the second one reflects a hypertrophied left atrium and is displayed by the apex increased in duration and amplitude (*Fig. 5*).

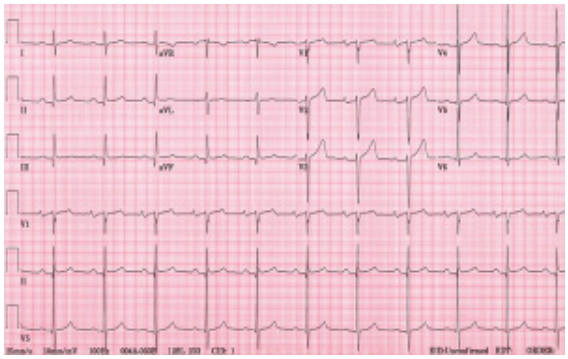

Fig. 5. Left Atrial Hypertrophy

ECG findings show the following:

1. A wide (more than 0.1–0.12 seconds in duration), two-humped P-wave with an interval between apices more than 0.02–0.04 seconds in left leads (I, II, AVL, $V_{5–6}$)

2. A negative, wide, two-humped P-wave in AVR.

3. P-wave ECA deviation to the left (α = -30°–90°), with a high-amplitude P-wave in lead I and formation of the ratio: P I> P II> P III.

4. In V_1, the P-wave is displayed as a negative or diphasic (+/-) wave with significant (>1 mm deep), wide (0.04 seconds and more) negative portion.

The Macruz index may serve as an additional LAH confirmation criterion:

P-wave (seconds) / PQ segment (seconds)	In presence of the right atrial hypertrophy, it will be more than 1.6.

LAH criteria for the standard ECG and cardiac computed tomography findings were compared suggesting that, among all the diagnostic criteria, the increased P-wave duration (more than 0.11 seconds) showed the highest sensitivity (71%) and specificity (55%), other parameters did not have sufficient diagnostic accuracy [34]; however, in 2014, sensitivity was demonstrated to increase with simultaneous presence of two criteria (P-wave duration > 0.12 seconds and its diphasic nature in V_1), its specificity was up to 100% [35], studies continued in 2016 with experimental voxel-based biatrial models and demonstrated directly associated, statistically significant correlations between the left atrial wall thickness and increase in the second phase duration of the P-wave in V_1 (more than 0.4 seconds) [36].

ECG signs of Left Ventricular Hypertrophy

In presence of left ventricular hypertrophy (LVH), excitation vector of the interventricular septum and ventricles increases and shifts to the left, which is displayed in ECG as increase in QRS complex amplitude in left leads, and ECA shift to the left. In this situation, repolarization processes in the thickened left ventricular (LV) and interventricular septal walls progress slowly and start at the endocardium, leading to an ECG left-to-right change in the repolarization vector and shift of the ST segment below an isoline in left leads and above an isoline in right leads extending to a concordant, asymmetric T-wave (*Fig. 6*).

ECG findings show the following:

1. In limp leads:

R I ≥ 15 mm; R AVF >20 mm; R AVL>11 mm; Q or S AVR>19 mm;

R I+ S III >25 mm (Gubner index); (R I- S I)+(S III- R III) >16 mm (Lewis index).

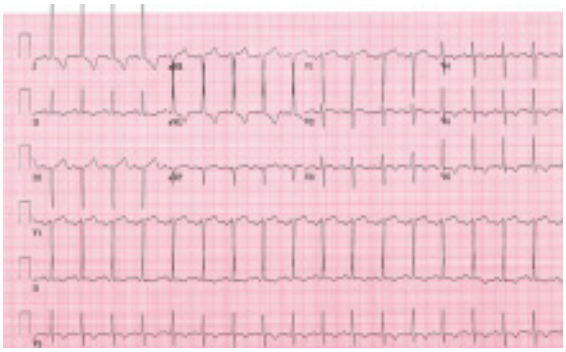

Fig. 6. Left Ventricular Hypertrophy

2. In precordial leads:

S V_1 >23 mm; S V_2 >25 mm; R V_5 >33; R V_6 >25 mm;

S $V_1(V_2)$ + R $V_5(V_6)$ >35 mm for individuals of over 40, and S V1(V2) + R $V_5(V_6)$ >45 mm for individuals under 40 (modified Sokolow-Lyon index)

3. Combined criteria (precordial and limb leads):

RS AVF +V_2 +V_6 >59 mm for individuals over 30 and RS AVF +V_2 +V_6 >93 mm for individuals under 30;

S V_3 +R AVL >28 mm for men, and S V_3 +R AVL >20 mm for women (Cornell voltage index)

(S V3 +R AVL)* QRS (ms) for men, and (S V3 +R AVL+8)* QRS (ms) for women >2400 mm*ms (Cornell product) [31.37]

Additional criteria are believed to include:

The ratio for the R-wave: R I> R II > R III; R V_6 ≥ R V_5 ≥ R V_4; ECA deviation to the left; insufficient R-wave amplitude buildup in right precordial leads, in presence of a deep, occasionally wide S-wave; the S segment changes displayed as downsloping depression in V_5, V_6.

The Romhilt-Estes score system is also known; the following parameters are used for assessment: [38]

• R or S amplitude in any limb lead ≥ 20 mm • S V_1 or SV_2 amplitude ≥ 30 mm • R V_5 or V_6 amplitude ≥ 30 mm	3 scores
ST segment or T-wave discordant to the QRS complex in V_5 or V_6 • without digitalis administration • with background digitalis administration	 3 scores 1 score
P-wave: presence of a negative deep (≥ 10 mm) and prolonged (≥ 0.4 seconds) wave in V_1	2 scores
ECA deviation to the left (α angle ≤ -30°)	2 scores
QRS duration ≥ 0.09 ms	1 score
Time of internal deviation V_{5-6} ≥ 0.05 ms	1 score
According to the Romhilt-Estes score system, 5 or higher scores suggest presence of LVH, 4 scores suggest possible LVH, 3 and lower scores suggest low likelihood of LVH.	

Despite availability of numerous LVH identification criteria, they display quite low sensitivity (10.5%–68%) with high specificity (89%–99%) [39–42].

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THE ROLE OF TRACE ELEMENT SELENIUM IN CARDIOVASCULAR DISEASE DEVELOPMENT (REVIEW)

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Abstract

Balanced levels of trace element selenium are of high importance for many of the body's regulatory and metabolic functions. Reduction in selenium supply in humans can lead to an increased risk of various pathologies, including cardiovascular diseases. This article considers the contemporary opinions on the role of selenium in physiology and pathophysiology of the cardiovascular system. A particular attention is payed to the effects of selenium deficiency on the development of acute coronary syndrome, including myocardial damage after ischemia/reperfusion and postinfarction remodeling of the left ventricle. Also, the intrinsic properties of selenium for inhibition of apoptosis are highlighted.

Keywords: *selenium, selenoproteins, cardiovascular disease.*

The data of the latest research suggest that disturbance in the metabolic balance of several trace elements can contribute to development and prognosis of cardiovascular disease (CVD) [23]. These minerals include selenium, a microelement, which possesses significant biological activity and a narrow profile of safety, and is important for human health. Selenium was first discovered by a Swedish scientist Berzelius in 1818. The biological function of selenium is determined by its position in the periodic system and is closely related to the chemical properties of this element and its compounds [1].

In humans, as well as in animal experiments, spontaneous or experimental reduction in selenium supply can lead to an increased risk of various pathologies, including CVD. Selenium deficiency, which is usually a result of alimentary shortage, demonstrates a particularly negative influence in geochemical provinces with low selenium content in the soil. The most reliable sources of selenium in the human diet are the following: seafood, animal liver, meat, cereals, and vegetables – garlic, onion, cabbage (especially broccoli) [2]. According to the recommendations of the Food and Drug Administration (FDA) of the United States, the daily need for selenium is 50–200 mg. At the same time, a prolonged excessive (over 400 mg/day) consumption of selenium performs a toxic effect on human body.

Selenium mediates its effects mainly due to inclusion to various selenoproteins. More than 25 selenium proteins are known at present. These include the group of glutathione peroxidase enzymes (GPO), iodothyronine deiodinase (ITD), thioredoxine reductase (TRR), selenoproteins (SP), K, R, S, O, W and others. A wide range of biological functions is characteristic for the majority of selenium-dependent enzymes, such as the regulation of the inflammatory response, the proliferation and differentiation of some immune cells, maintenance of thyroid hormones balance, spermatogenesis, etc. [17]. Selenium is an important factor for biological protection of vascular endothelial cells, DNA, and chromosomes. It is an extremely important nutrient for the prevention of coronary heart disease (CHD). Selenium inhibits atherosclerosis development and suppresses malignant tumors

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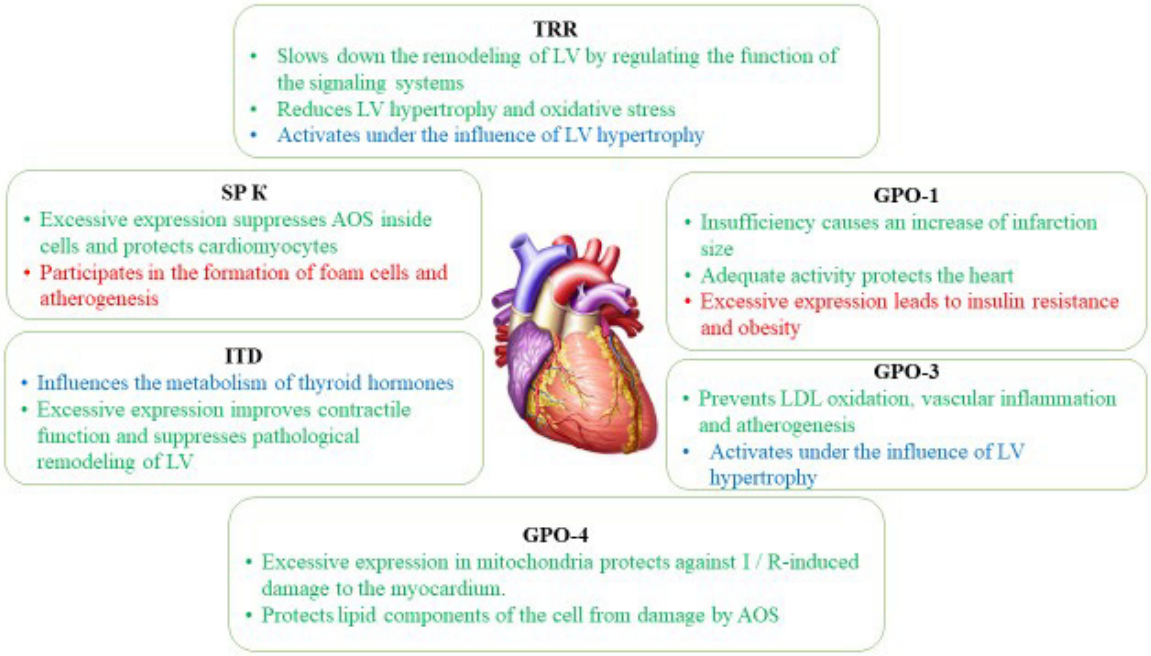
formation [5]. Selenium is considered to be the cornerstone of the body's antioxidant defense. Selenium acts only as an antioxidant and almost never behaves as a prooxidant, unlike other metals with variable valence [2]. In addition, previous studies have shown that selenium compounds can affect, and thus control the function of leukocytes: migration, adhesion and phagocytosis [4]. The main aspects of selenoproteins influence on the function of the cardiovascular system (CVS) are shown in *figure*.

The influence of selenium on development and prognosis of cardiovascular diseases is performed in several ways, the main path is the activation of the antioxidant system. The current research data suggest that excessive formation of reactive oxygen species (ROS) plays an important role in the pathogenesis of CVD, such as coronary heart disease and heart failure. When excessive ROS formation exceeds the potential of endogenous antioxidant defense system, an oxidative stress develops, causing adverse effects on the myocardium, including the decrease of contractility and ultrastructural changes [18]. Trace elements such as selenium mainly prevent ROS-induced damage to cells by increasing the activity of antioxidant enzymes.

The most studied group among selenoproteins is GPO, which provides neutralization of active forms of oxygen and nitrogen, thereby limiting myocardial damage after ischemia/reperfusion (I/R). Lubos E. et al. have proved that the low level of GPO1 in erythrocytes significantly increases the risk of cardiovascular events, such as myocardial infarction and stroke [12]. TRR also plays an important role. It exerts the regulatory influence on the cardiovascular system, due to the oxidation of intracellular and extracellular signaling molecules [14] and the impact on adaptive mechanisms, such as left ventricular remodeling [3]. According to G. Flores-Mateo, selenium levels in the blood reversely correlate with the risk of CHD development [7]. At the same time, the AtheroGene study revealed no effect of low selenium concentrations on the development and progression of stable angina, but it has shown that selenium deficiency is associated with an increased risk of cardiovascular death in patients with acute coronary syndrome [13].

The exact role of other selenoproteins in support of the cardiovascular system function as well as in the possible development of CVD is only partially understood. It is believed that most selenoproteins act as antioxidants that regulate various signaling processes by influencing the oxidation-reduction homeostasis and intake of calcium ions Ca2+ into the cell [17]. In particular, it has been proved that selenoprotein K is involved in the mechanisms of antioxidant defense of cardiomyocytes [11]. In this regard, K. Venardos et al. demonstrated in experiments in rats that the



The role of selenoproteins the CVS functioning: GPO – glutathione peroxidase, TRR – thioredoxine reductase, ITD – iodothyronine deiodinase, SP – selenoproteins, LV – left ventricle, LDL – low density lipoprotein, AOS – active oxygen species, I / R – ischemia / reperfusion.

deficiency of selenium leads to an increase of myocardial damage by increasing the peroxidation of proteins and lipids after I/R [21]. These data have been further confirmed by Tanguy and co-authors, who have shown that selenium deficiency in rats leads to more significant myocardial damage and delayed heart function recovery after I/R [20]. The same research groups demonstrated a significant positive effects from supplemental selenium provision (using selenium-containing drugs or high-selenium diet), which were the following: decrease of myocardial damage as a result of I/R, better restoration of the contractile function, reduction of the infarction size and the decrease of frequency of post-ischemic ventricular arrhythmias. The main causes for these results remain only partly understandable and cannot be explained solely by the antioxidant properties of selenium and its compounds. Therefore, there is a need for additional research to further study the effects of selenium on the functioning of the cardiovascular system.

In addition to antioxidant action, selenium has intrinsic properties for apoptosis inhibition. Experimental studies conducted on different types of cells report very heterogeneous results. However, the data of S. Mukherjee and co-authors is worth paying attention. They have shown that a high-selenium diet has a cardioprotective effect and reduces the damaging effect of ischemia and reperfusion by generating an anti-apoptotic signal through the activation of several survival proteins, such as Akt and Bcl-2 [16]. Another argument in favor of the anti-apoptotic effect of selenium was provided by studies in animals that were accompanied by artificial suppression of selenoproteins synthesis. Research by P. Crack et al. [6] on GPO-1-knockout mice showed that GPO-1 plays an important regulatory role in protecting nerve cells from apoptosis induced by I/R. In addition, it has been shown that ischemic stress in astrocytes activates the gene expression of selenoprotein S, and inhibition of the expression of this gene by small interfering RNAs significantly increases astrocytes apoptosis in ischemia [8]. These results indicate that the optimal expression of selenoproteins is a key factor for survival signaling under oxidative stress conditions.

Cardioprotective properties of selenium are also associated with its ability to suppress the cascade of nuclear factor-kappa B transformations (NF-κB). Increased activation of transcription factor NF-κB is usually associated with survival signals in cardiomyocytes, as well as in other cell types. However, a prolonged and excessive formation of ROS can lead to activation of proinflammatory and proapoptotic pathways through disbalance between tyrosine kinase and tyrosine phosphatase, which regulate the translocation of NF-κB [10] Therefore, over-stimulation of NF-κB in myocardium during ischemic episodes leads to the increased production of cytokines and tumor necrosis factor – alpha (TNF-α). Selenium reduces nuclear translocation of NF-κB during myocardial infarction in rats, it also decreases the size of myocardial injury and inhibits post-ischemic TNF-α production. Selenoprotein S can directly interact with the inflammatory process, and thus limit the formation of cytokines [15].

An important function of selenium is the ability to reduce dephosphorylation of connexin-43 (Cx-43). Excessive ROS formation and following tyrosine kinase activation can lead to dephosphorylation of Cx-43 (this protein is responsible for intercellular communication and an electrical bond between cardiomyocytes), which is a determining factor in progression of cell death and thus affects the size of myocardial infarction and left ventricle post-infarction remodeling. Adequate supply of selenium to the body suppresses Cx-43 dephosphorylation, reduces the incidence of post-reperfusion arrhythmias, limits the size of infarction and inhibits cardiac remodeling [19].

Apart from the numerous positive effects of sufficient selenium supply, it makes sense to consider the aspects of its toxic effects, which occur at long-term excessive intake of this trace element. Chronic selenium overdose can lead to negative consequences for the body as a whole and for CVS in particular. The long-term overdose of selenium increases the risk of type 2 diabetes and dyslipidemia [9]. Excessive expression of GPO-1, as well as other selenoproteins, which possess antioxidant action, causes development of insulin resistance and obesity due to distortion of the course of oxidation-reduction reactions and changes in the functioning of the intracellular and extracellular signaling systems [22]. The excessive concentrations of selenium have the ability to accumulate in the form of selenomethionine in various tissues and organs, including the heart. Replacement of methionine with selenomethionine changes stability of proteins, in particular, it affects calmodulin, which may alter calcium metabolism in cardiomyocytes and cause negative consequences for the processes of contraction and relaxation of the myocardium [24].

Conclusions

Thus, recent studies have created a significant evidence base on the important role of selenium and its compounds in the cardiovascular system functioning. Although the data on the role of selenium in CVD prevention remain controversial, it is important to establish the impact of selenium deficiency on the course and prediction of an acute coronary syndrome, in which the patient is exposed to ischemia/reperfusion and the rapid activation of oxidative stress. Therefore, the relationship between selenium ingestion, selenium content in the body and the state of the cardiovascular system requires additional experimental evidence in order to provide a new understanding of the role of selenium in the biology of human heart. Further studies should be performed to find out the main mechanisms that associate selenium provision to the body with the end points of the CVD, and also to determine the influence of selenium on cardiovascular risk factors.

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COMPARISON OF MODIFIED METHOD OF LIGATION OF INTERSPHINCTERIC FISTULA TRACT (LIFT) AND STANDARD OPERATIONS IN PATIENTS WITH TRANSSPHINCTERIC RECTAL FISTULAS

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Abstract

Background. The search for and development of new minimally invasive methods for the surgical treatment of anal fistulas is a relevant area of surgery. Such methods combine less traumatization and preservation of the sphincter's complex. Employment of such methods for surgical treatment of anal fistulas reduced the time of stay of patients in the hospital and improved their quality of life. **Subjects and methods.** A retro- and prospective study involved 58 patients with uncomplicated transsphincteric anal fistulas. All patients were treated in the hospital from January 2014 to April 2019. The patients were divided into two groups: the first group included 32 patients who were operated on according to the standard procedure using fistulotomy and Seton procedure; the second group consisted of 26 patients who were operated on using the modified LIFT method. **Results.** Most of these patients (72.4%) were men at the age of 42.53 6.79. The median of BMI was 25.7 kg/m2. There wasn't mortality after operations. The median follow-up was 21 (6–48) weeks. In the first group there were 3 cases (9.3%) of anal sphincter insufficiency and 7 cases of recurrent fistulas (21.9%) at different times after surgery. In the second group there were no anal sphincter failure following administration of the modified method LIFT, but there were 15.4% of recurrent anal fistulas. **Conclusion.** The proposed modified method of ligation of intersphincteric fistula tract is an effective method for the treatment of anal fistulas. The results obtained suggest that the developed method can be used to treat other types of anal fistulas.

Keywords: *transsphincteric anal fistula, surgical treatment, LIFT technique, postoperative complications*.

Introduction

Rectal fistula (anal fistula, fistula-in-ano, chronic paraproctitis) is a pathological course or cavity connecting the lumen of the anal canal or rectum with the perineum. The main clinical manifestations of the disease are mucopurulent discharge in this area, pain syndrome, discomfort, which significantly reduces the patient's quality of life [1]. According to foreign literature, the prevalence of rectal fistula in European countries is 10.4–3.2 persons per 100,000 population [2]; this disease is more common among men than in women with a ratio of 1.8: 1 [3]. Reticular fistulas are diagnosed in patients of different ages, but most often they occur in the age group of 30–50 years [4], that is, in the most able-bodied and socially active part of the population. In 2016 in Sweden, Lundqvist A. et al. conducted a study to evaluate the cost of rectal fistulas treatment in 362 patients. The authors have shown that the total cost of patient treatment amounted to an average of 5561 euros, of which 80% were direct

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medical expenses for treatment. The remaining 20% were economic losses associated with the duration of the period of disability, an average of 10.4 days [5]. It should be noted that such a high cost of treatment was due to the high number of recurrences and development of complications.

Rectal fistulas rank fourth in the structure of proctological diseases. This disease can be treated only surgically. Among all proctologic operations, from 13.6 to 25.4% of operations to eliminate fistulas are performed each year [6, 7]. The most common cause of perianal fistula is inflammation of the anal glands in the anal crypt area, followed by the spread of infection to the adrectal tissue. The infection can also penetrate through the damaged lymphogenous and hematogenous rectal mucosa. Chronic recurrent anal fistulas are due to the lining of the internal hole of the fistula with the glandular epithelium of the anal glands and the subsequent complete or partial epithelization of the lumen of the fistulous passage, preventing its spontaneous healing.

There are more than one hundred methods of surgical treatment of fistulas of the rectum, but there is still no single "gold standard". The main components of the surgical treatment of fistulas are the excision of the fistulous course, the elimination of purulent infections and the provision of wound healing [8–12]. Considering the involvement of the anal sphincter in the pathological process, the most important is the preservation of its functional ability. That is why the search for new minimally invasive methods of surgical treatment remains relevant.

2. Purposes, subjects and methods:

2.1. Purpose – was to compare and to analyze the standard methods of surgical treatment of anal fistulas with the modified method of ligation of intersphincteric fistula tract (LIFT) that we developed in our clinic.

2.2. Subjects & Methods

A retro- and prospective study involved 58 patients with uncomplicated transsphincteric anal fistulas. All patients were treated in the hospital from January 2014 to April 2019. The patients were divided into two groups. The first group included 32 patients who were operated with the standard methods. The standard procedures included fistulotomy and Seton techniques. The second group (the remaining 26 patients) were operated with the modified method LIFT.

Identification of patients, operative technique and postoperative period

The inclusion criterion was the diagnosis of transsphincteric anal fistulas. In all patients, this diagnosis was made for the first time. Exclusion criteria were the presence of surface fistulas, as well as fistulas associated with Crohn's disease. Patients with concomitant pathology of the rectum were excluded from the study.

After the diagnosis was made, the patients underwent laboratory and instrumental examinations. Laboratory methods included standard tests and bacteriological examination of purulent contents of the fistula. Instrumental examination methods included anoscopy, rectoromanoscopy, fistulography and MRI. Preliminary identification of the fistulous course was necessary to define the localization of the fistula. It also helped to determine the presence of purulent cavities. The patients diagnosed with uncomplicated fistulas were included in the study.

The proposed method is a modification of the classical technique of LIFT. First the fistulous duct was contrasted. Then the distal part of the fistula was excised at the probe. Then a probe was inserted through the internal opening of the fistulous passage and a fistula was fixed on it. After that, the intra sphincter part of the fistula was inverted into the rectal lumen and ligated closer to the intestinal mucosa. The operation was performed under spinal anesthesia. An antibacterial prophylaxis was administered for 24 hours.

In the postoperative period all patients received analgesics and syrups softening feces. Postoperative care included the use of antiseptic baths, dressing with ointment and rectal suppositories. We have identified main parameters in order to compare the results of surgical treatment. There were such parameters as recurrence of the disease, functionality of the anal sphincter, terms of wound healing, days at the hospital stay. The procedure was considered successful in complete wound healing, absence of insolvency of the anal sphincter or recurrence of the disease. In the event of fistula recurrence the result of treatment was regarded as unsatisfactory. Postoperative complications and mortality were evaluated in all the examined patients.

In order to assess the quality of treatment, all patients underwent follow-up examination. Similar examinations were carried out every 2 weeks after discharge from the hospital in the first two months after surgery. After that monitoring of the results of surgical treatment was carried out for 3 to 12 months. We conducted a survey and clinical examinations of patients at each visit in order to clarify presentation and complications.

Conflict of interests. There is no conflict of interests.

3. Results and discussion

The characteristics of patients who were studied are presented in the *Tables 1* and *2*. The first group included 23 men (71.8 %) and 9 women (28.2%), the second group comprised 19 men (73.1%) and 7 women (26.9%). The age of the patients was 42.53±6.79, mean body mass index (BMI) was 25.7, concomitant diseases were noted in 9 (15.5%) patients. In the first group of patients, simple fistulas were diagnosed in 8 and complex in 24 patients, and in the second group, 7 and 19 patients, respectively. The distance between the external opening of the fistula and the anus was 4.5±0.93 cm.

Table 1

Characteristics of patients who participated in the study

Characteristics under investigation	Indicators obtained
Number of patients	58
Males (%)	42 (72.4%)
Females (%)	16 (27.6%)
Average age	42.53±6.79
Median BMI (kg/m^2)	25.7
Accompanying diseases (%)	9 (15,5%)
Previous operations (1st/2nd)	7 (4/3)
Type of fistula (%) and the complexity of the fistula in groups (simple/complex)	58 patients (100%): 1st – 8/24; 2nd –7/19
Distance between the external hole of the fistula and the anus (cm)	4.5±0,93

Table 2

Grouping by sex and age

Age of patients	First group (n=32)				Second group (n=26)			
	Males		Females		Males		Females	
	Per.	(%)	Per.	(%)	Per.	(%)	Per.	(%)
25–44	9	28.12	2	6.25	7	26.92	3	11.53
45–60	11	34.37	5	15.64	8	30.76	3	11.53
61–70	3	9.37	2	6.25	4	15.38	1	3.88
Total	23	71.86	9	28.14	19	73.06	7	26.94

Among the patients in the first group 23 (71.8%) patients underwent excision of the anal fistula with admissible sphincterotomy without disturbance the function of the closure of the sphincter complex of the rectum. In 8 of these patients the operations was supplemented with sphincteroplasty. The remaining 9 patients (28.2%) underwent Seton techniques of the anal fistula. After evaluating the results of surgical treatment of patients from the first group, 84.4% of cases were found to be satisfactory. The result of treatment was unsatisfactory in 10 patients (31.2%) out of 32 operated. Of these, 7 (21.9%) patients had a recurrence of the disease and other 3 patients had sphincter deficiency in all periods of observation. Postoperative complications were observed in 4 patients (12.5%). All complications were resolved with the help of conservative treatment. The patients of the second group were operated with the modified method of LIFT. Treatment was satisfactory in 22 patients (84.6%). Anal fistula recurred in 4 patients (15.4%). Anal sphincter insufficiency was not registered in this category of patients. Two patients had complications in postoperative period (7.7%). These complications were also resolved with the help of conservative treatment methods.

All the results of treatment for all 58 patients are shown in the *Tables 3* and *4*.

As can be seen from the Table 4, patients operated with modified method LIFT reduced the days of hospital stay. The postoperative hospital stay of such patients averaged 12.3 days.

In such patients, the healing time of the wound was also shorter. The average duration was 26.1 days. This can be explained by the less traumatic nature of the proposed method.

Table 3

Comparative results of treatment

Comparative parameters	Results	
	Standard methods	**LIFT**
Operation duration, minutes (median, min, max)	50.5 (39–72)	49.6 (35–67)
Satisfactory result of treatment (%)	84.4%	84.6%
Recurrence of fistulas (%)	7 (21.9%)	4 (15.4%)
Sphincter deficiency (%)	3 (9.4%)	0
Postoperative complications	4 (12.5)	2 (7.7%)
Postoperative mortality	0	0
Observation after surgery, weeks (median, min, max)	24 (2–48)	18 (2–48)
Time of fistula recurrence, month (median, min, max)	7.5 (4–24)	18 (8–24)

Table 4

Comparative results of surgical treatment

Comparative parameters	Groups of patients			
	1st (n=32)			2nd (n=26)
	Sphincterotomy	Sphincterotomy with sphincteroplasty	Seton technique	LIFT
Number of patients	15	8	9	26
Operation duration (min)	48.1	55.8	58.4	49.6
Recurrence of fistulas	3	2	2	4
Sphincter deficiency	1	1	1	0
Terms of wound healing (days)	29.7	27.4	41.4	26.1
Days of the hospital stay	14.2	13.7	17.1	12.3
Postoperative mortality	0	0	0	0

If simple anal fistulas do not present great difficulty in diagnosis and treatment, and also accompanied by a small percentage of complications after surgery, complicated fistula is a frequently discussed topic in clinical practice. Many surgical methods have been described for the treatment of such anal fistulas, including Seton technique, fibrin glue, collagen closures, rectal valves, fistulotomy with regeneration of the sphincter and redirecting the fistulous tract [13]. However, the results were variable and no procedure exceeds the other altogether. It is worth worrying that the purpose of any treatment is to destroy the path and reduce the frequency of relapses while maintaining the full functionality of the anal sphincter complex. The fistulotomy opens the fistula path, leaving less wounds without epithelization, which accelerates healing of the wound. Currently, fistulotomy is still the most widely used method. But the high rate of treatment is limited by the fact that the incidence of fetal incontinence can be up to 40% [14] when transphasic fistula is opened and the internal and external sphincter is cut. The most important factor when choosing an adequate method of operation is known to be the relationship of the fistulous passage to the fibers of the sphincter apparatus of the rectum. The most reliable method of surgical treatment of complex fistulas is its excision or dissection into the lumen of the rectum. Sphincterotomy is an effective way to treat anal fistulas. But if the fistula spreads to most of the sphincter complex, the operation may contribute to insolvency of the anal sphincter in the postoperative period. In the surgical approach to dissection/excision of the fistula, some authors take into account the degree of involvement of the sphincter apparatus by no more than 10-20%; others no more than 33%. Therefore, this operation requires appropriate selection of patients.

In 2007, Rojanasakul et al. described a new surgical variant for such cases with very good

initial results. Since then, LIFT has been used as a remedy for sphincter, to restore anal fistulas through early satisfactory results. Today there are more than 6 variants of the LIFT. However, the success rate varies from 47 to 95% [15, 16]. This can be explained by the fact that some methods are based only on ligation of the fistulous tract without its excision. There was no comparative study between the methods at this time. That is why it is difficult to determine the true value of both the classic technique and its modifications. We are confident that the success of the operation depends on the identification of the fistulous tract and its excision. It should also be noted that the excision of the fistulous tract in the intersphincteric space reduces the risk of development of the anal sphincter deficiency. Since direct comparison between technical variants was not made, it remains difficult to find out the true effectiveness of the classic LIFT or any of its technical varants [17]. Thus, the technique of LIFT without incision of the fistula is a minor modification of the operation [8]. The indicator of success in 47-94.2% was reported using this LIFT technique [18]. We are convinced that success after this operation depends on the proper identification of the fistula and the processing of its distal part without damage, as well as the reliable treatment of the internal hole of the fistula. Currently, there may be some controversy over the definition of failure after surgery, persistence and recurrence of anal fistula after surgery. In any case, success after the LIFT procedure can be objectively defined as complete postoperative healing, both the fistula outlet and the wound between sphincters. Finally, recurrence can be considered as a recurrence of fistula after complete healing of the wound [19].

In our study, there were 3 cases (9.3%) of anal sphincter failure with the use of fistulotomy and Seton technique and 7 cases of recurrent fistulas (21.9%) after these interventions at different times after surgery. The modified LIFT technique was not associated with any anal sphincter failure, but 15.4% of recurrent anal fistulas were observed in these patients. We analyzed the results and identified the main causes of recurrence and insufficiency of the anal sphincter. The first group included mistakes associated with preoperative diagnosis. Incomplete fistula contrasting contributes to incorrect determination of the course of the fistula relative to the fibers of the anal sphincter. This is why some authors recommended using MRI [20] which we used before the operation only in 3 patients of the second group. This method helps to determine purulent pararectal foci, and also get the complete information on the condition of the anal sphincter complex and guarantees the correct choice of surgical procedures. Among the technical mistakes we noted two main ones. Firstly, excessive excision of the anal sphincter tissue during fistula discharge. Secondly, wound suppuration which contributes to the failure of the sutures. These factors lead to the formation of a coarse postoperative scar that reduced the functional ability of the sphincter.

Some authors suggested the use of drainage before the LIFT procedure as an effective remedy for failure after surgery, although this was not mentioned in the original descriptive publication. But studies show that previous use of drainage before LIFT did not affect the performance indicators and in analyzing the combined data of four studies of patients undergoing LIFT with preoperative drainage and without it, no significant difference was observed with the previous drainage [21, 22]. Nevertheless, the results presented should be interpreted with caution since in some cases the initial design of the study was not aimed at studying or comparing the results of patients with or without drainage.

We achieved 84.6% of successful wound healing after the modified method of LIFT. We consider this technique promising since its implementation does not require expensive materials. It is necessary to continue research on the modified method of LIFT. This will help to identify shortcomings and also help to improve the methods of surgical treatment with complex transsphincteric fistulas of the rectum.

Conclusions. Minimally invasive surgical methods are a promising direction in proctology. The modified technique LIFT is an effective method of surgical treatment of transsphincteric fistulas of the rectum. The operation that we proposed is simple to perform. It does not require the use of expensive materials and therefore, this method is profitable with economic component. The advantage of the method is to preserve the quality of life. A high level of successful operations indicates the prospect of use of this method in the treatment of fistulas of other types.

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FORENSIC MEDICAL EXAMINATION IN NON-FATAL LARYNGEAL TRAUMA

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Abstract

Victims with non-fatal laryngeal trauma become the object of forensic medical evaluation of the severity of bodily injuries in alive persons, carried out during pre-judicial and judicial investigation. The purpose of the study was to provide morphological and clinical analysis and characteristics of bodily injuries in cases of blunt laryngeal trauma in forensic medical examination of alive persons, to determine ways to improve the effectiveness of forensic medical diagnosis of the specified injury. **Subjects and Methods.** The study involved morphological and clinical analysis of 47 forensic medical expert conclusions in the leading forensic medical examination institution of Kharkiv region. **Results.** Frequency and types of blunt traumas of the larynx at examination of alive persons were determined. Specific features of forensic medical expert evaluation of bodily injuries severity in alive persons with blunt traumas of larynx were determined. Severe bodily injuries were defined in 3 cases (6.4 % of cases) of laryngeal traumas with the development of mechanical asphyxia. Moderate bodily injuries were determined by experts in 9 cases (19.1 % of cases) of blunt traumas of the larynx, accompanied by fractures of its cartilage; in 4 persons (8.5 % of cases) of blunt traumas of the larynx, accompanied by hematoma, edema of soft tissues of the larynx; in one case of blunt laryngeal trauma with acute edema, its second-degree stenosis. Mild bodily injuries which caused short-term disorder in 25 persons (53.2 % of cases) and mild bodily injuries which caused slight transitory effects in 4 persons (21.1 % of cases) were determined by experts in forensic medical examination of blunt laryngeal trauma with the development of acute posttraumatic laryngitis. The study implied elaboration of methods and an algorithm for improvement of forensic medical diagnostics in this type of injuries. **Conclusions.** Medico-legal diagnosis of blunt laryngeal trauma can be associated with underestimation and overestimation of the severity of bodily injuries by experts, which requires further research in the field of establishing unbiased expert diagnostic criteria for assessing such injuries.

Keywords: *criteria of diagnosis, forensic medical examination, expert conclusion, laryngeal trauma.*

Introduction

Laryngeal traumas are characterized by open and closed injuries, such as stabbed, incised, stabbed-incised wounds, ruptures of organ walls, fractures and dislocations of laryngeal cartilages frequently accompanied by life-threatening signs and require an accurate medico-legal evaluation [1–4]. Such consequences of laryngeal traumas, as its stenosis and phonation dysfunction, result in loss of the working capacity [3, 5]. At the same time, victims with non-fatal laryngeal injuries become the object of forensic medical evaluation of the severity of bodily injuries in alive persons, carried out during pre-judicial and judicial investigation [6, 7].

Determination and substantiation of medico-legal diagnostic criteria is regarded as an actual and perspective direction of scientific research in forensic medicine, which would allow to objectively and comprehensively define the kind of trauma, the mechanism of its development and

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to estimate the severity of bodily injuries in each particular case [8–10]. "Rules for forensic medical assessment of bodily injuries severity" [11] (the Order of the Ministry of Health of Ukraine No.6 as of 17.01.1995) do not contain, and, probably, should not contain the full list of diagnostic criteria for definition of clinical features in each possible damage. They also do not contain the optimum list of diagnostic tests which should be carried out for an objective estimation of the severity of bodily injuries. It leads to underestimation of severity of bodily injuries by practical forensic medical experts, especially by those with little practical experience, resulting in appointment of a repeated forensic medical examination, usually by a medical expert board.

A review of literature [12–15] on examination of alive persons, written by leading scientific forensic medical physicians, shows that there have been no thorough scientific studies on determination and substantiation of diagnostic criteria for medico-legal estimation of the severity of bodily injuries in laryngeal injuries. Besides, closed non-fatal blunt laryngeal injuries are the most difficult for expert evaluation, which is related to the variety of their complications and consequences.

2. Purposes, subjects and methods:

2.1. Purpose – was to provide morphological and clinical analysis and characteristics of bodily injuries in blunt laryngeal trauma in forensic medical examination of alive persons, to determine ways to improve the effectiveness of forensic medical diagnosis of the specified injury.

2.2. Subjects & Methods

The materials were the conclusions of forensic medical examination on blunt laryngeal trauma (BLT) in alive persons that were conducted with our participation at Kharkiv Regional Bureau of Forensic Medical Examination (KRBFME) in 2005–2018. Moreover, the study involved assessment of archival expert conclusions for the specified period of time at the Department of Forensic Medical Examination of Victims, Accused and Other Persons of KRBFME. In total, 47 cases of forensic medical examination of BLT were processed retrospectively.

The study implied the following methods: registration method, the data were written on a specifically designed registration card that included a list of relevant morphological and clinical features; standard methods of the descriptive statistics; morphological method, the nature of the damage was determined; clinical, dysfunction of larynx, duration of impairment was analyzed; forensic medical examination, severity of bodily injuries was evaluated by experts.

During examination, oral consent was obtained from all victims. The written consent from victims during forensic medical examinations should not be provided, according to the regulatory documents governing their performance. This study is permitted by the ethics and bioethics commission of Kharkiv National Medical University.

Conflict of interests. There is no conflict of interests.

3. Results and discussion

The study showed that in annual quantity of traumas of the neck BLT occupies 0.6% of expert examinations at the Department of Forensic Medical Examination of Victims, Accused and Other Persons of KRBFME. At the same time, 24 expert examinations (51.1% of cases), including laryngeal injuries, included male patients, and 23 expert examinations (48.9% of cases) female patients. Besides, 18 patients (38.3% of cases) were of working age (20–50 years old). As for the mechanism of development, 25 patients (53.2 % of cases) received shock blow by blunt solid objects onto the neck (more often, blows by fingers of arms, clenched into a fist, and other blunt solid objects), in 20 patients (42.6 % of cases) compression of the neck by arms, in 2 patients (4.3% of cases) compression of the neck by arms and a loop. In general, low incidence of BLT in victims was confirmed by few, and in some cases durable, up to several decades, cases of such injuries, by individual authors [1, 2, 6]. At the same time a fourfold prevalence of such injuries in males was observed, which differs from our observations.

The character of damages detected during forensic medical examination was as follows. In 42 patients (89.3% of cases) ecchymosis, grazes, specifying the place of traumatic force, were detected on the neck. Two patients (4.3% of cases) had strangulation mark and grazes on the neck. In 3 patients (6.4% of cases) no visible damages were found on the neck, which complicated medico-legal examination.

Damages of the larynx in victims were as follows: all the victims had symptoms of acute post-traumatic laryngitis of varying severity. Thus, 9 patients (19.1% of cases) were found to have hemorrhages and edema in vocal cords, their mobility impairment in phonation, hyperemia, edema of mucous membranes in the epiglottis.

Fractures of laryngeal cartilage, either cricoid or thyroid, or of both laryngeal cartilages were

diagnosed in 9 patients (19.1 % of cases). At the same time, one patient had hematoma on the right half of the neck and first-degree stenosis of the larynx. In two cases, the larynx was deformed due to its cartilage integrity disruption. Two patients (4.2% of cases) were found to have disruption of thyroid-hypoglossal membranes integrity, edema, hemorrhages in vocal cords, loss of their mobility in phonation, hemorrhage of the mucous membrane. One patient (2.1% of cases) had a fracture of the left superior horn of thyroid cartilage with a shift, and edema of soft tissues in the area of the thyroid cartilage.

Moreover, 15 patients (31.9% of cases) had hematoma and edema of soft tissues of the larynx. Five patients (10.6% of cases) were found to have narrowing of the larynx, due to life-threatening swelling of soft tissues. One patient (2.1% of cases) had hematoma, edema of soft tissues in the region of arytenoid cartilages and vocal cords with vocal dysfunction. One patient (2.1% of cases) had hematoma, acute edema of the larynx, second-degree stenosis of the larynx with dysfunction of its neuromuscular apparatus, hemorrhage in the epiglottis and in the parapharyngeal fat.

There was a case of BLT that deserves special attention: a 6-year-old girl received an injury by a compression of the neck by the loop and arms in which, besides the ligature mark and grazes on the neck and acute posttraumatic laryngitis, experts also diagnosed signs of mechanical asphyxia. She was found to have a gradually progressing dysfunction of the central nervous system, resulting from cerebral circulation disruption in the pool of the right middle cerebral artery. The first symptoms in the form of clonic convulsions appeared in 2 days after the injury, and, in 15 days tetraparesis developed. As an outcome of the trauma, the girl had left-sided hemiparesis.

In 3 patients (6.4% of cases), one with fractures of the laryngeal cartilage and one with acute posttraumatic laryngitis, BLT was complicated by the development of perichondritis of its cartilages. In 4 patients (8.5 % of cases) BLT resulted in acute posttraumatic laryngitis, chronic laryngitis, and in 4 patients (6.4% of cases) BLT with hematoma of the larynx was associated with posttraumatic paresis of laryngeal muscles.

It is noteworthy that in the medical documentation given to experts and accordingly in expert opinions the emphasis is not always placed on the type of inflammatory process in the larynx (catarrhal, purulent, purulent-necrotic). In fractures of laryngeal cartilages, the character of fracture, presence and degree of fragments shift are not emphasized. Also, the emphasis is not placed on presence and character of luxations of laryngeal cartilages most commonly observed in cricoarytenoid joints and rarer in cricothyroid joints. Insufficient diagnosis of cartilage damage in cases of BLT is also indicated in some studies [6, 7]. The character of the specified changes can influence the severity of bodily injuries. Computed tomography, which can detect damages of laryngeal cartilages, is not always included in diagnostic procedures performed as a part of examination. At the same time, the importance of computed tomography in such cases is emphasized both in the scientific work of clinicians and forensic medical experts [3, 8]. In certain examinations, no additional tests, including those determining the degree of laryngeal dysfunction, were performed. Advising otolaryngologists, was involved only in one case in performing primary examinations and in 2 cases in examination provided by medical expert board.

In medico-legal expert examination the severity of bodily injuries in BLT was defined as follows: severe bodily injuries, by

"life-threatening" criterion according to the "Rules", were defined in 3 cases (6.4% of cases) of laryngeal traumas with the development of mechanical asphyxia.

Moderate bodily injuries, by "impairment duration" criterion of more than 21 days, according to the "Rules", were estimated by experts in 9 patients (19.1% of cases) with BLT accompanied by fractures of its cartilage; in 4 patients (8.5% of cases) of BLT accompanied by hematoma, edema of soft tissues of the larynx; one case of BLT was accompanied by acute edema, second-degree stenosis of the larynx, neuromuscular apparatus dysfunction, hemorrhages in the epiglottis and parapharyngeal fat. The duration of impairment, defined in these examinations, was confirmed by results of objective methods of examination and time course of pathological changes. In our opinion, the full duration of impairment and outcomes of larynx traumas are considered only in these examinations.

Mild bodily injuries, which caused short-term impairment of more than 6 days and less than 21 days, were defined in 25 patients (53.2% of cases). In these cases, BLT was accompanied by acute posttraumatic laryngitis, which in 6 cases was associated with hemorrhages in vocal cords, in 10 cases with posttraumatic hematoma of the

larynx. Besides, only in 23 cases the severity of injury corresponded to these criteria and the "Rules", and in 2 cases it did not because the patients were treated for more than 21 days. In our opinion, when treatment of patients with acute posttraumatic laryngitis took longer than 21 days, the experts should have performed additional medico-legal diagnosis and estimated the outcome correctly. And, probably, the severity of bodily injuries would be qualified as moderate.

Mild bodily injuries which caused slight transitory effects, lasting not more than six days, were established by experts in 4 patients with BLT (21.1 % of cases), with the development of acute posttraumatic laryngitis, wherein, in 3 cases it was accompanied by hemorrhages in vocal cords, and in one case by perichondritis of laryngeal cartilages. In these examinations experts did not have enough information about outcomes of laryngeal injury necessary for medico-legal evaluation of bodily injury severity. Additional control diagnostic tests were not conducted by experts during examinations as well. In these cases, because of the absence of information on trauma outcomes and impossibility to perform additional tests by experts it was necessary to refuse from defining the severity of bodily injuries.

In 2 patients (4.3% of cases) with BLT experts have refrained from evaluating the severity of bodily injuries because of the unbearable outcome of trauma with the development of acute posttraumatic laryngitis, hyperemia, edema of the mucous membrane of epiglottis and vocal cords.

Along with some contradictions in forensic medical expert opinions on the forensic medical evaluation of BLT severity, as shown by the review of special literature [7, 10, 15], the views of forensic scientists on the application of certain qualifying signs from normative documents also differed. In particular, there were contradictory views on what kind of BLT should be considered as a life-threatening.

The results of our study allowed us to develop an algorithm-program for carrying out scientific research on determination and substantiation of medico-legal diagnostic criteria of BLT severity which contains the following stages:

• assessment of presentation and outcomes of laryngeal traumas according to the "Rules". The conducted assessment helped to identify medico-legal diagnostic criteria of BLT severity;

• determination of BLT incidence, its presenting signs and outcomes based on the assessment of archival medico-legal records;

• comparison of the data received following the assessment of medico-legal archival records with clinical findings. Interpretation of the received data;

• carrying out forensic medical examination simultaneously with comprehensive clinical examination of the patients;

• substantiation of medico-legal diagnostic criteria for determination of the severity of bodily injuries in BLT.

Conclusions

1. Accurate medico-legal diagnostic criteria for blunt laryngeal traumas have not been defined so far, which occasionally leads to arbitrary interpretation of the "Rules" by experts, in definition of the severity of bodily injuries.

2. Non-life-threatening blunt laryngeal traumas prevail in medico-legal practice in examination of alive persons and require careful medico-legal estimation of outcomes and consequences that can cause difficulties for medico-legal experts.

3. In certain examinations experts underestimated severity of bodily injuries while determining blunt laryngeal traumas, and in some other examinations severity was overestimated.

4. During medico-legal examination, the complex of modern examination methods for definition of the character and outcome of blunt laryngeal traumas was not used by experts to the full extent.

5. It is necessary to perform further research in the field of medico-legal analysis of all possible clinical and morphological signs, outcomes of laryngeal traumas, in order to determine and substantiate diagnostic criteria for defining the severity of bodily injuries.

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PECULIARITIES OF DRUG-RESISTANT TUBERCULOSIS IN UKRAINE AND KHARKIV REGION

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Abstract

Background. Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis remain severe epidemic problems in the world.

Therefore the **purpose** of our study was to investigate the dynamics of the incidence of multidrug-resistant and extensively drug-resistant tuberculosis, the structure of cases and the effectiveness of treatment in this category of patients in Kharkiv region and Ukraine. **Subjects and methods.** To perform the study, data from reporting forms No. 4–2 (TB 07 – MDR TB), No. 8-6 (TB 08) and data from Kharkiv region and from other regions of Ukraine were processed. The form "TB 07 – MDR TB" shows the total number of MDR-TB and XDR-TB cases; new cases, relapses and other cases of re-treatment among them; number of MDR-TB and XDR-TB cases in which anti-tuberculosis treatment started. The form "TB 08" shows treatment results in MDR-TB and XDR-TB cases. We investigated MDR-TB and XDR-TB cases detected in 2015–2017. Statistical processing of information was carried out using Microsoft Office Excel 2010. **Results.** The stable dynamics of drug-resistant tuberculosis incidence at the level 12.3–12.5 per 100000 population was found in Kharkiv region while in Ukraine this parameter increased from 15.9 to 19.7 per 100000 population. In the structure of MDR-TB and XDR-TB cases, patients with firstly diagnosed tuberculosis prevailed: 46.7–54.4% in Kharkiv region and 45.0–51.2% in Ukraine. The patients with acquired drug resistance had relapse of tuberculosis or other cases of repeated treatment more often and in Kharkiv region their percentage prevailed significantly ($p<0.01$). Treatment effectiveness of firstly diagnosed drug-resistant tuberculosis (58.2% in Kharkiv region and 55.8% in Ukraine) was significantly higher ($p<0.01$) than treatment effectiveness of cases of repeated treatment (45.4% in Kharkiv region and 38.6% in Ukraine).**Conclusions.** Early introduction of new effective molecular-genetic and cultural methods of drug-resistance diagnosis in Kharkiv region allowed to detect most of drug-resistant TB cases while in other regions of Ukraine these methods were introduced later that caused increase in MDR-TB and XDR-TB incidence during observation period. Domination of firstly diagnosed MDR-TB and XDR-TB cases indicates critical epidemiological situation, as there are many undetected cases of drug-resistant tuberculosis that can infect people and increase incidence of primary resistant tuberculosis. Higher treatment effectiveness in Kharkiv region can be explained by accessibility of new antituberculous second-line drugs. Thus, wide introduction of methods of early drug-resistance detection and accessibility of new antituberculous drugs improve epidemiological situation on tuberculosis in Kharkiv region compared with other regions of Ukraine.

Keywords: *Tuberculosis, MDR-TB, XDR-TB, treatment effectiveness.*

Introduction

In 2015, the WHO announced the "End TB" strategy for overcoming the epidemic of tuberculosis in the world. According to the objectives of this strategy, it is necessary to reduce the mortality rate by 95% and the incidence rate by 90% by 2035. To do this, it is necessary to achieve the effectiveness of treatment of tuberculosis with a preserved sensitivity of 85% and multidrug-resistant tuberculosis – 75% [1].

However, drug-resistant tuberculosis, and in particular multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB),

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is now a complex epidemiological problem in the world. According to the WHO, in 2017, there were 160,684 new cases of MDR-TB and XDR-TB, which is 4.9% more than in 2016. Of these, only 87% of patients began treatment with second-line anti-TB drugs. At the same time, the effectiveness of the treatment of drug-resistant tuberculosis is only 55% [2].

In the Eastern European region, 9 countries with the highest burden of MDR-TB include Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, Tajikistan, Ukraine and Uzbekistan. According to the WHO reports, all patients in the region had access to second-line drugs [3]. At the same time, one of the five cases of MDR-TB in the world is registered in European Region. The average effectiveness of treatment for MDR-TB in the region is 51% [4].

2. Purposes, subjects and methods:

2.1. Purpose – to investigate the dynamics of the incidence of multidrug-resistant and extensively drug-resistant tuberculosis, the structure of cases and the effectiveness of treatment in this category of patients in Kharkiv region and in Ukraine.

2.2. Subjects & Methods

The observation period 2015–2017 was chosen because treatment results can be evaluated only in 18–20 months according to MDR-TB and XDR-TB treatment regimens (2017–2019 respectively). Kharkiv region was chosen for the detailed analysis due to both high population density and migration that causes favorable conditions for the tuberculosis distribution.

On the other hand, there it is an appropriate access to the TB diagnosis and treatment that can control of tuberculosis in the region. Kharkiv region is among first ones that supported innovations in the framework of the National Tuberculosis Control Program. Therefore, each patient has access to molecular-genetic methods for diagnosing tuberculosis and M.tuberculosis resistance (GeneXpert MTB/RIF, Hain MDR TB), new cultural diagnostic methods (BACTEC MGIT 960), new anti-tuberculosis drugs for the treatment of drug-resistant tuberculosis. To perform the study, data from reporting forms No. 4–2 (TB 07 – MDR TB), No. 8–6 (TB 08) from Kharkiv region and from other regions of Ukraine were processed. The form "TB 07 – MDR TB" shows the total number of MDR-TB and XDR-TB cases; new cases, relapses and other cases of re-treatment among them; number of MDR-TB and XDR-TB cases in which anti-tuberculosis treatment started. The form "TB 08" shows treatment results in MDR-TB and XDR-TB cases. The proportion of resistant forms among various types of tuberculosis cases was calculated. Types of tuberculosis cases were determined in accordance with the Order of the Ministry of Health of Ukraine No. 620 as follows: firstly diagnosed tuberculosis (FDTB) – patients who had not previously been diagnosed with tuberculosis and who had not received anti-tuberculosis treatment previously, relapse of tuberculosis (RTB) – patients who successfully completed earlier treatment for tuberculosis, other cases of re-treatment – treatment after interruption, treatment after treatment failure, and other cases that are not included in the classification. The treatment was considered as effective when the bacterial excretion stopped and the severity of clinical and radiological manifestations of the disease was decreased. Resistance type was determined as multidrug-resistant tuberculosis (MDR-TB) – resistance to isoniazid and rifampicin (main first-line drugs) and extensively drug-resistant tuberculosis (XDR-TB) – resistance to isoniazid, rifampicin, one of the fluoroquinolones and one of the aminoglycosides. Statistical processing of the information was carried out by using Microsoft Office Excel 2010.

Ethics approval and consent to participate

An epidemiological study was performed using standard reporting forms, without the direct participation of patients. Personal data were not used and the consents were not signed.

Conflict of interests. The authors declare that they have no competing interests.

3. Results and discussion

The dynamics of the incidence of MDR-TB and XDR-TB in Kharkiv region was analyzed; a stable level of 12.3–12.5 per 100 000 population in 2015 and 2017 and a sharp increase in the incidence of up to 13.8 per 100 000 population in 2016 were revealed. In Ukraine, this level was 15.9 per 100 000 population in 2015 and steadily grew by 15.1% in 2016 (18.3 per 100 000 population) and by 23.9% in 2017 (19.7 per 100 000 population).

Since the sources of multidrug resistance and extensively-drug resistance may be primary infection with resistant strains (primary resistance), as well as the acquisition of secondary resistance due to the recurrence of tuberculosis with a second course of tuberculosis chemotherapy, treatment failure or treatment interruption, the proportion of different cases

among patients with drug-resistant tuberculosis was investigated.

According to the type of case (first diagnosed tuberculosis or relapse of tuberculosis) in Kharkiv region, patients were distributed as follows: in 2015, the proportion of patients with FDTB was 46.7%, patients with RTB – 29.1%, patients with other cases of repeated treatment – 21.2%. In 2016, there was a significant increase in the proportion of patients with FDTB – 54.4%, RTB – 32.2% (p = 0.04) and a decrease in the proportion of patients with other cases of repeated treatment – 13.4% (p = 0.01). In 2017, the proportion of patients with FDTB was 57.4%, RTB – 28.9%, other cases of re-treatment – 13.7%.

In Ukraine, there was a similar trend. In 2015, FDTB accounted for 45.0% of cases, RTB – 29.6%, and other cases of re-treatment – 25.4%. In 2016, patients with FDTB accounted for 50.1%, with RTB – 31.1%, with other cases of repeated treatment – 18.8%. In 2017, FDTB – 51.2%, RTB – 30.9%, other cases of re-treatment – 17.9% (*Fig. 1, 2*).

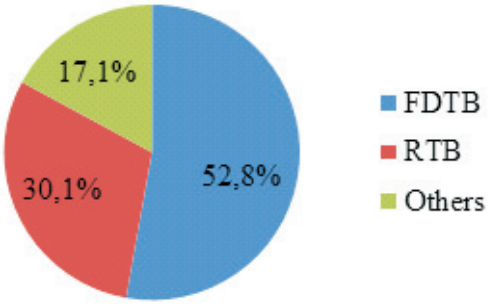

Fig. 1. Distribution of various cases of tuberculosis among patients with drug-resistant in Kharkiv region
FDTB – firstly diagnosed tuberculosis
RTB – relapse of tuberculosis

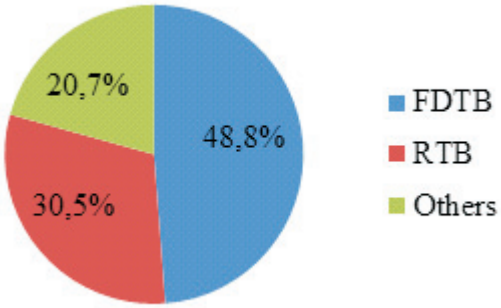

Fig. 2. Distribution of various cases of tuberculosis among patients with drug-resistant in Ukraine
FDTB – firstly diagnosed tuberculosis
RTB – relapse of tuberculosis

The difference between Kharkiv region and Ukraine in distribution of various cases of tuberculosis among patients with drug-resistance was found only in part of other cases of re-treatment in 2016 (p = 0.01) and FDTB cases (p = 0.03) in 2017. The difference was insignificant (p>0.05) in other cases.

We analyzed the proportion of patients with the primary susceptible tuberculosis (first diagnosed or relapsed) with acquired drug resistance, who transferred to the treatment by the second-line drugs. In Kharkiv region, there was insignificant increase in the percentage of patients with FDTB in whom M. tuberculosis (MTB) developed acquired drug-resistance (2015 – 17.3%, 2016 – 21.6%, 2017 – 22.6% (p = 0.09)) and with other cases of repeated treatment (2015 – 30, 8%, 2016 – 32.3%, 2017 – 33.1%). The worst situation with a slightly positive trend was observed in patients with RTB (2015 – 59.4%, 2016 – 57.1%, 2017 – 51.1% (p = 0.03)). Thus, we can see that acquired drug resistance is usually developed in patients with relapses of tuberculosis and other cases of re-treatment (p < 0.01).

In Ukraine, there was a similar situation. Among patients with FDTB, 14.2% of patients were transferred to treatment with second-line drugs in 2015, in 2016 – 18.3%, in 2017 – 18.0%. The proportion of patients with other cases of re-treatment transferred to treatment with second-line drugs was: in 2015 – 23.5%, in 2016 – 18.3%, in 2017 – 27.1%. Patients with RTB were transferred to treatment with second-line drugs in 2015 – 43.3% of cases, in 2016 – 41.9%, in 2017 – 43.7% (*Fig. 3*).

The part of TB relapses and other cases of the re-treatment among the cases of acquired drug-resistance are significantly prevalent in Kharkiv region (p < 0.01).

We also analyzed the distribution of both types of resistance (MDR-TB and XDR-TB) and their dynamics in Kharkiv region.

Among the patients with FDTB, in 2015 MDR-TB accounted for 91.3%, XDR-TB – 8.7%, in 2016 – 90.7% and 9.3%, in 2017 – 90.7% and 9.3% respectively.

Among the patients with RTB, in 2015 MDR-TB accounted for 87.2%, XDR-TB – for 12.8%, in 2016 – 90.7% and 9.3%, in 2017 – 77.7% and 22.3%, respectively.

Among the patients with other cases of re-treatment, in 2015 MDR-TB accounted for 89.4%, XDR-TB – for 10.6%, in 2016 – 79.1% and 20.9%, in 2017 – 75.6% and 24.4 % respectively. (*Fig. 4*).

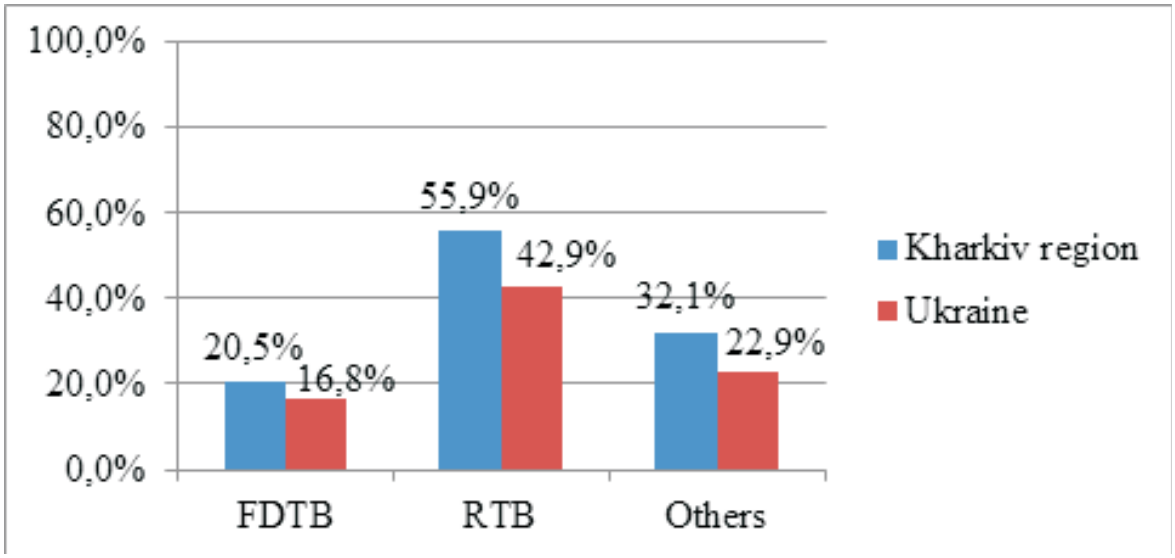

Fig. 3. The proportion of patients with various cases of tuberculosis that were transferred to treatment with second-line drugs: FDTB – firstly diagnosed tuberculosis, RTB – relapse of tuberculosis

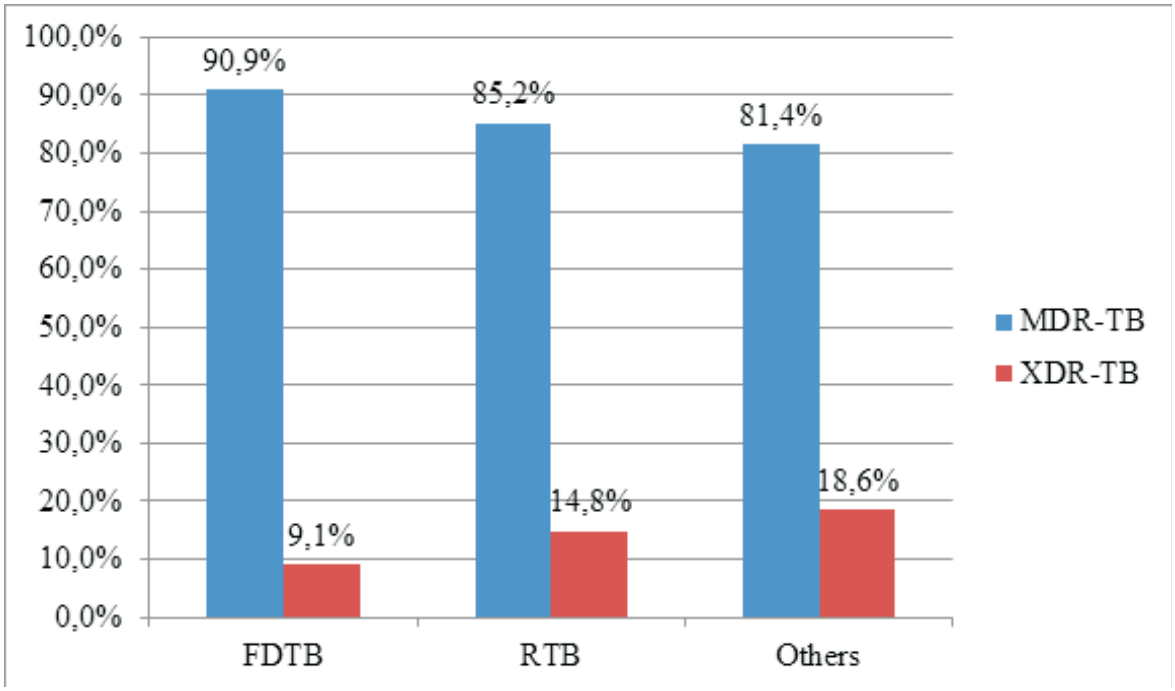

Fig. 4. The structure of M. tuberculosis resistance in patients with various cases of tuberculosis: FDTB – firstly diagnosed tuberculosis, RTB – relapse of tuberculosis, MDR-TB – multidrug-resistant tuberculosis, XDR-TB – extensively-drug resistant tuberculosis

Thus, we can see that XDR-TB is observed in cases of relapses and re-treatment more often than in FDTB cases ($p < 0.01$).

Since MTB resistance profile is directly related to the effectiveness of treatment, the effectiveness of treating various cases of tuberculosis in patients transferred for treatment with second-line drugs in Kharkiv region was compared.

The effectiveness of treatment of MDR-TB among FDTB was: in 2015 – 56.9%, 2016 – 65.8%, 2017 – 51.8% with a corresponding mortality rate of 21.8%, 12.1% and 14.5%. The effectiveness of treatment of MDR-TB among RTB was: in 2015 – 54.3%, 2016 – 60.0%, 2017 – 60.4% with a corresponding mortality rate of 26.8%, 13.8% and 19.8%. The effectiveness of treatment of MDR-TB among other cases of repeated treatment was: in 2015 – 33.5%, 2016 – 33.3%, 2017 – 30.8% with a corresponding mortality rate of 31.6%, 28.0% and 15.4% (*Fig . 5*).

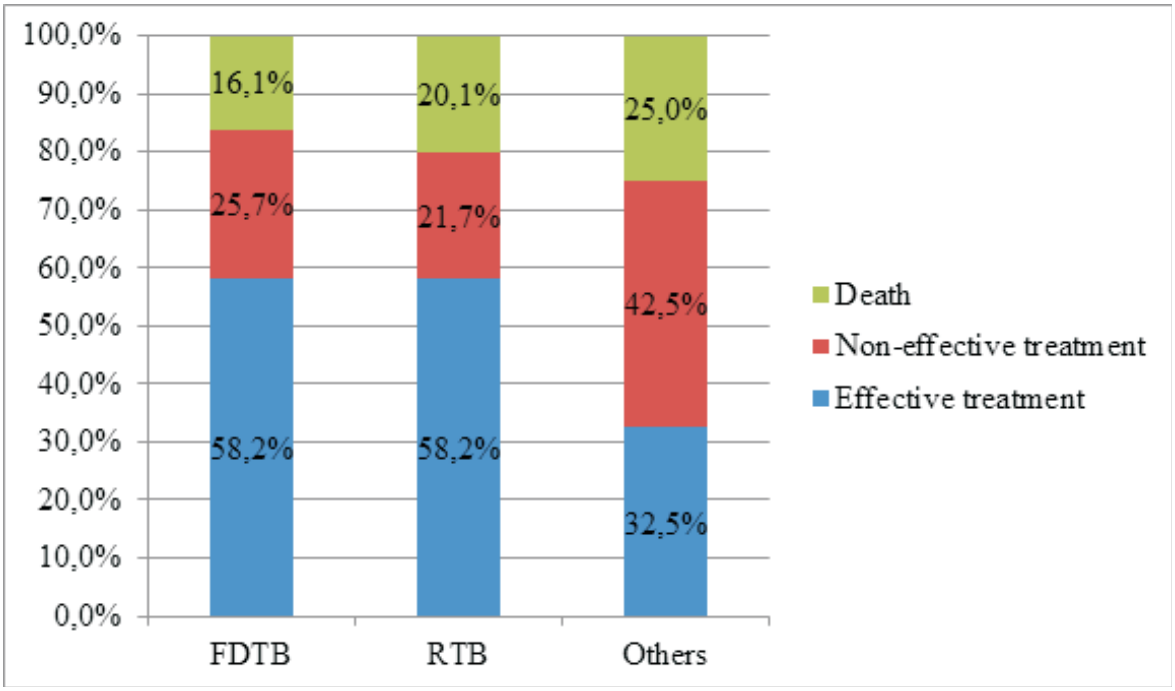

Fig. 5. Efficacy of MDR-TB treatment in patients with various types of tuberculosis cases: FDTB – firstly diagnosed tuberculosis, RTB – relapse of tuberculosis

There was no difference between MDR-TB relapse and FDTB cases treatment effectiveness ($p > 0.05$) but the treatment effectiveness of other cases of repeated treatment was significantly lower ($p < 0.01$) which led to higher case fatality rate in this group ($p = 0.01$).

We compared the treatment effectiveness in patients with different types of MDR-TB and XDR-TB in Ukraine. The effectiveness of treatment of the firstly diagnosed MDR-TB cases significantly increased from 50.6% in cases detected in 2015 to 55.8% in 2016 and to 61% in 2017 ($p < 0.01$) with a corresponding case fatality rate of 16.8%, 15.3% and 14.2% which also significantly decreased ($p < 0.01$). The effectiveness of treatment of relapsed cases of MDR-TB in 2015 was: 33.2%, in 2016 – 39.9%, in 2017 – 42.7% ($p < 0.01$) with a corresponding case fatality of 24.0%, 17.7% and 16.8% ($p < 0.01$). Treatment effectiveness of FDTB MDR-TB cases was significantly higher ($p < 0.01$) than in cases of repeated treatment with corresponding lower case fatality rate ($p < 0.01$).

XDR-TB treatment effectiveness in patients with FDTB is significantly increased from 37.9% cases detected in 2015 to 43.1% – in 2016 and to 51.2% – in 2017 ($p < 0.01$) with the corresponding fatality rate – 16.7%, 18.2% and 20.0%, relevantely. XDR-TB treatment effectiveness in patients with the relapses did not changed significantly and was 28.2% in 2015, 21.5% in 2016 and 32.4% in 2017 ($p=0.12$) with a corresponding case fatality rate – 21.4%, 27.7% and 0, relevantely (*Fig. 6, 7*).

Treatment effectiveness of the newly diagnosed MDR-TB cases was significantly higher ($p < 0.01$) but the case fatality rate in new cases and cases of re-treatment was almost same ($p = 0.14$).

Discussion. MDR-TB and XDR-TB remain a serious problem not only in Ukraine, but all over the world [5–9]. However, the increase in the incidence of drug-resistant tuberculosis in Ukraine can be explained not only by a poor epidemiological situation, but also by improved diagnosis, since now molecular-genetic research methods such as GeneXpertMTB/RIF and rapid culture methods of research (BACTEC) have become available even to the residents of remote villages. In Kharkiv region, the widespread introduction of rapid methods for diagnosing drug-resistance became available as early as 2013–2014, thus a stable incidence rate of drug-resistant tuberculosis among residents of Kharkiv region was received.

But the direct evidence of the unfavorable epidemiological situation of drug-resistant tuberculosis in the country was the determination of the structure of tuberculosis cases. It turned out that among patients with MDR-TB and XDR-TB, primary drug resistance prevailed and increased, that is, MTB resistance to anti-tuberculosis drugs in patients who had never received anti-tuberculosis treatment before. It means that epidemiological situation on drug-

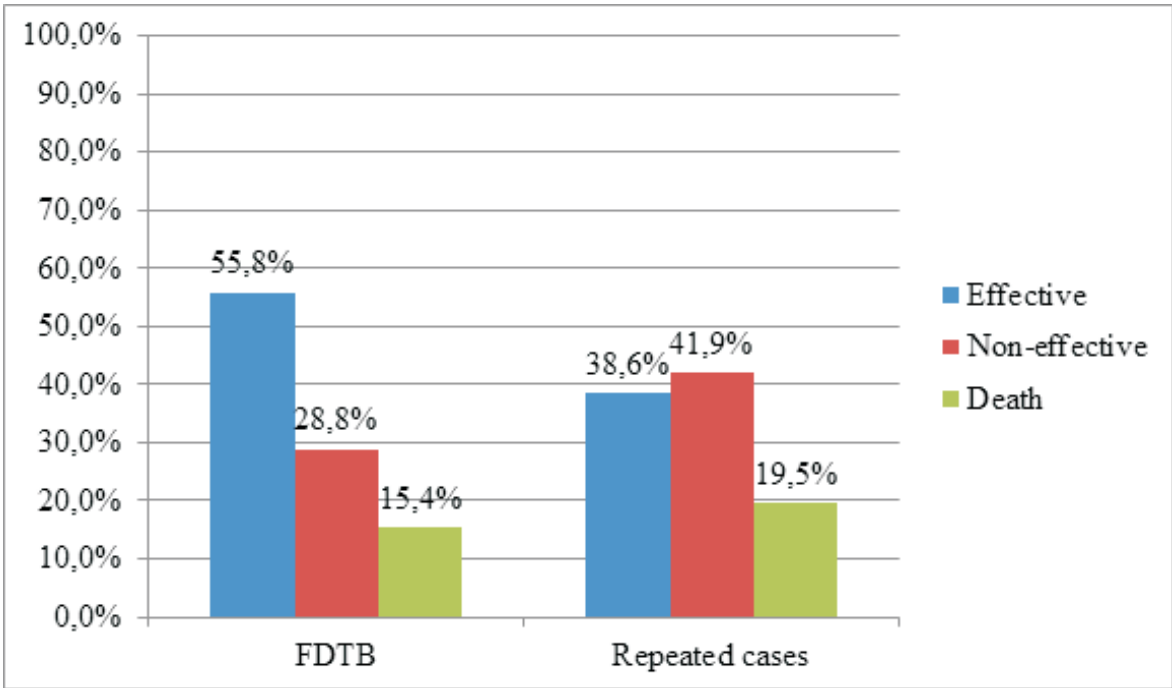

Fig. 6. Treatment effectiveness of MDR-TB: FDTB – firstly diagnosed tuberculosis

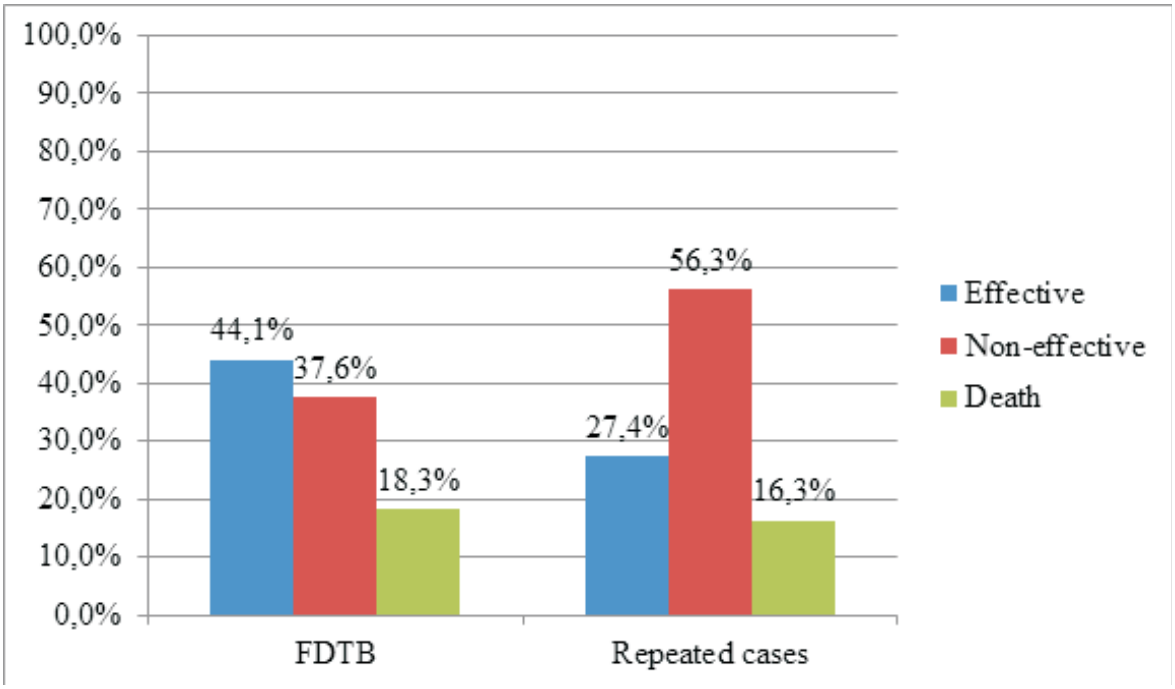

Fig. 7. Treatment effectiveness of XDR-TB: FDTB – firstly diagnosed tuberculosis

resistant tuberculosis in both Kharkiv region and Ukraine is critical so that non-detected patients with drug-resistant tuberculosis infect healthy people in household and casual contacts and increase part of firstly diagnosed MDR-TB and XDR-TB. Similar problem was also observed in number of other countries, that worsens the prognosis of treating patients and indicating an unfavorable epidemiological situation [10–12].

One of the key moments in preventing development of drug-resistance is administration of the effective chemotherapy regimen to the patients with tuberculosis. We have noticed that patients who started treatment from susceptible tuberculosis develop drug resistance more often after the relapse of tuberculosis or another case of the re-treatment (after treatment failure of treatment interruption). The repeated treatment

course is resulting treatment failure in both Kharkiv region and Ukraine. It was assumed that it happens due to the fact that the MTB has enough time to acquire drug resistance during the second course of treatment. The situation is aggravated by the fact that for the treatment of FDTB and RTB, the same regimens and the same treatment duration are used, which increases the chances of the MTB for the development of drug-resistance [13–17]. Now we can propose treatment regimens with new antituberculous drugs (Bedaquiline and Delamanid) for these patients in Kharkiv region but results of new treatment regimens can not be evaluated yet.

Interesting data were obtained by analyzing separately the proportion of patients with MDR-TB and XDR-TB. Although a greater amount of acquired drug-resistance falls on the recurrence of tuberculosis, most of the XDR-TB account for other cases of re-treatment, including treatment failure and interrupted treatment. This means that the main link in the prevention of the expansion of M.tuberculosis resistance is the administration of the adequate chemotherapy regimens and strict adherence by patients to the rules for administering anti-tuberculosis drugs. Effectiveness of administration of appropriate treatment regimens as well as introduction of more effective antituberculous drugs (new fluoroquinolones, Linezolid) is confirmed by the growth of newly-diagnosed XDR-TB cases treatment effectiveness.

Conclusions

The drug-resistant tuberculosis incidence was stable in Kharkiv region and increased in Ukraine during the observation period due to the fact of the new effective methods of drug resistance diagnosis (BACTEC MGIT 960, GeneXpert MTB/RIF, Hain MDR TB), that were introduced in Kharkiv region earlier and allowed to detect most of MDR-TB and XDR-TB cases.

Newly diagnosed MDR-TB and XDR-TB cases are prevailed in both Kharkiv region and Ukraine that means we still have many non-detected cases that can infect people and increase the incidence of primary resistant tuberculosis.

Acquired drug-resistance among patients with newly diagnosed tuberculosis was observed in Kharkiv region less often than in Ukraine. It can be explained by the earlier introduction of new anti-tuberculosis drugs in Kharkiv region as well as by accessibility of methods of early drug-resistance detection. These factors lead to the increase of treatment effectiveness.

It was proven that repeated courses of treatment after the treatment failure due to treatment interruption regardless of the resistance profile result in treatment failure or death more often. Therefore, introduction of new anti-tuberculosis drugs that can decrease number of first-course treatment failures and introduction of short treatment regimens for MDR-TB cases that can decrease number of treatment interruptions is a priority of the Ukrainian National Tuberculosis Control Program.

List of abbreviations:

FDTB – firstly diagnosed tuberculosis
RTB – relapse of tuberculosis
MDR-TB – multidrug-resistant tuberculosis
XDR-TB – extensively drug-resistant tuberculosis
TB – tuberculosis

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FEATURES OF THE CLINICAL COURSE OF ROTAVIRUS INFECTION IN CHILDREN INFECTED WITH HERPES VIRUSES AND THEIR BLOOD INTERLEUKIN REACTIONS

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Abstract

Background. The widespread prevalence of intestinal infections of rotavirus etiology, the economic damage caused by it and the difficulties of treating patients cause the medical and social significance of this pathology. Along with this, a herpes virus infection and its negative effect on the immune response of the human body is a pressing problem. The purpose of the study is to identify the characteristics of presentation and the course of rotavirus infection in children infected with herpes viruses, and to establish the characteristics of the reaction of interleukins in their blood. **Subjects and Methods**. 38 children aged one to three years with moderate and severe forms of intestinal infection rotavirus etiology, who received appropriate treatment were examined. The children were divided into two groups: Group 1 included 18 children who did not have a background infection and Group 2 comprised 20 patients with acute rotavirus infection who were infected with herpes viruses. Along with the generally accepted clinical and laboratory examination, the levels of interleukins 1β, 4, TNFα in the blood serum in the time course of the disease were determined by an ELISA method for all children. **Results.** Assessment of clinical and immunological parameters of rotavirus infection in children showed that infection with viruses of the herpes group contributed to a less severity of symptoms of the disease at the initial stage, but longer persistence, which was probably due to insufficient reaction of proinflammatory interleukins in blood in the acute period at relatively high levels during the course of the disease.

Keywords: *clinic, children, cytokines, herpes and rotavirus infections.*

Introduction

Intestinal infections (II) are among the most common children diseases [1, 11]. Their etiological structure is extremely polymorphic. The causative factor of the disease may be protozoa, bacteria, fungi, viruses, etc. [14, 16, 20]. Studies conducted in recent decades proved the leading role of viruses in the development of II [3, 17]. Among them, the dominant role is played by rotaviruses (RV) [2, 3]. According to WHO statistics, about 125 million cases of rotavirus etiology are observed in the world every year, and over 500 thousand children under the age of 5 die from this pathology [4, 5].

The clinical picture of lesions of the gastrointestinal tract of rotavirus nature is rather brightly highlighted in the available literature [2, 3, 9]. However, many scientists have recently noted its significant changes [6, 7, 12]. Some authors attribute this to negative ecological state in many countries and the world as a whole, which contributes, firstly, to the change of the virus itself, and secondly, to the formation of immune-suppressive status in contemporary children [1, 18, 15]. Other researchers believe that changes in the clinical symptoms of rotavirus infection (RVI) are due to the additional infection of the child population, in particular, herpes viruses [10, 13, 19].

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At the same time, there are very few studies on clinical and immunological features of RVI in children infected with the herpes group in the available literature, and their results are very contradictory [8].

Meanwhile, in our opinion, research in this area will reveal the subtle pathogenic mechanisms of rotavirus pathological process in children infected with herpes viruses, which will allow to diagnose background infection in the early stages of the disease and more reasonably and convincingly to approach the treatment of patients.

2. Purposes, subjects and methods:

2.1. Purpose: to identify the features of presentation of rotavirus infection in children infected with herpes viruses, as well to establish the features of the reaction of interleukins in their blood.

2.2. Subjects & Methods

The study involved 38 children aged one to three years with moderate and severe forms of intestinal infection of rotavirus etiology, receiving appropriate treatment in Kharkiv Regional Children's Infectious Diseases Hospital. Of these, 18 (the first group) did not have a background infection and 20 (the second group) carried RVI against the background of infection with various herpes viruses. The children of these groups were comparable by sex, age, severity of the disease and other parameters.

RVI was confirmed using the separation of rotavirus antigen from fecal masses of patients by ELISA. The presence of herpes virus infection (1, 2, 4, 5, 6 types) was proved by the corresponding IgM and IgG classes in the blood (ELISA), or isolation of the virus nucleic acid by Polymerase chain reaction (PCR).

Children with the latent form of the herpes virus infection were included in the study. The latent form of herpes virus infection was established when specific class G antibodies (IgG) were detected in the titer above the diagnostic one in the absence of other markers (IgM-negative, PCR-negative) and clinical manifestations.

All children were also examined for the presence of other viral or bacterial pathogens causing intestinal infections (feces), patients with a positive result were excluded from the study. Along with the generally accepted clinical and laboratory examination, the levels of interleukins 1β, 4, TNFα in the blood serum in the course of the disease were determined for all children (the acute period is 1–2 days of illness and the recovery period is 6–9 days). The results of the Dr. Kirsanova T.O study (2007) were used as a control [21].

Standard statistics was used for the data analysis.

All research methods were conducted in compliance with legislation on human rights, in accordance with the current legislation of Ukraine and international ethical requirements.

Conflict of interests

There is no conflict of interests.

3. Results and discussion

Analysis of clinical data showed that in both groups of children, the disease mostly began acutely with an increase in body temperature, vomiting and frequent loose stools (*Table 1*).

The increase in body temperature in children of Group 1 varied on average within 39.11±0.19 ° C, while in Group 2 patients it was 38.44 ± 0.17 ° C ($p<0.05$). Catarrhal manifestations in the form of hyperemia of the mucous membrane of the oropharynx and serous discharge from the nose were observed almost equally often in the groups under investigation, which did not contradict the results of the clinical researcher O.V. Usachova (2013) [8]. The number of children not infected with herpes viruses was recorded from one to eight to nine days per day (6.23±0.28), while in children with background infection it was more often observed one to four times a day (3,28±0.39) $p<0.05$.

The stool particles were almost identical in children compared in groups ($p>0.05$), although the nature of calories was largely enterocolitic in patients infected with herpes viruses, which, according to some authors, may be due to a weakening of their immune response and systemic actions herpes viruses and, as a result, the involvement in the process of a larger segment of the intestinal tube [9, 10].

A comparative analysis of clinical observations showed that children who were not infected with viruses and herpes had more marked temperature reactions, with almost the same severity of catarrhal symptoms and diarrhea syndrome.

Follow-up of children in the time course of the disease showed differences in diseases in groups under comparison (*Table 2*).

The study showed that in children infected with herpes viruses, the body temperature ($p<0.05$), intestinal dysfunction ($p<0.05$) persisted longer, with almost the same, compared with patients not infected with the herpes group, the duration of catarrhal events and vomiting.

Considering the identified differences in the severity of clinical manifestations of RVI at the beginning of the disease and their duration over

Table 1

Incidence of the main clinical manifestations of RVI in children of the groups under investigation

Symptoms of RVI		Group 1 (n=18)		Group 2 (n=20)	
		Abs	%	Abs	%
Temperature reaction	37.0–37.9 ºC	2	11.1	4	20
	38.0–38.9ºC	6	33.3	13	72.2
	39.0–40.0 ºC	10	55.6	3	15
Catarrhal manifestation	Mucous hyperemia of the oropharynx	11	61.1	12	60
	Serous discharge from the nose	7	38.8	9	45
Frequency of vomiting (per day)	No vomiting	3	16.6	5	25
	1–4	8	44.4	12	60
	5 or more	7	38.8	3	15
Frequency of defecation (a day)	1–4	1	5.55	2	10
	5–8	8	44.4	12	60
	9 or more	9	50	6	30

Table 2

The duration of the main clinical symptoms of RVI in children in the groups under investigation

Symptoms of RVI		The duration of clinical symptoms (day)		Statistically significant difference (pt) P
		Group 1 (n=18) M ±m	Group 2 (n=20) M ±m	
Temperature reaction		3.11±0.61	4.06±1.33	p<0.05
Catarrhal manifestation	Mucous hyperemia of oropharynx	3.71±1.04	3.07 ±0. 8	p>0.05
	Serous discharge from the nose	3.32±1.06	3.07±1.04	p>0.05
Vomiting		2.52±0.08	2.35±0.05	p> 0.05
Intestinal dysfunction		4.36±0.25	6.12±0.82	p<0.05

time, we conducted studies to determine the strength of the interleukin response in children of the groups under comparison (*Table 3*).

It was found that the severity of the reaction of pro-inflammatory interleukins (IL-1β and TNF-α,) in children uninfected with herpes viruses was more pronounced at the onset of the disease (IL-1β – 62.382 ± 3.14; TNF-α - 58.32±4.61) than in children with additional infection (IL-1β 51.11±2.67; TNF-α-481±2.39) p <0.05. At the same time, the strength of the response of interleukin 4 was almost the same (p> 0.05). In our opinion, it is the more significant reaction of proinflammatory interleukins in children without background infection at the onset of the disease that may explain their more pronounced temperature response and probably a greater frequency of vomiting. By the reconvalescence period, the levels of proinflammatory blood interleukins in patients with background infection remained significantly higher than in children not infected with herpes viruses. The latter seems to be a marker of not fully completed pathological process and an argument explaining the prolongation of clinical symptoms, in favor of which higher IL-4 numbers may indicate in the period of early recovery of children who have an additional infection.

Table 3

The level of blood interleukins in children of different groups during the course of the disease

Interleukins (pg/ml)	Periods of the disease	Group 1 (M±m)	Group 2 (M±m)	Healthy children (pg/ml) (M±m)
1β	acute	62.82±3.14	51.11±2.67	26.41±2.31
	reconvalescence	28.55±2.22	40.06±1.92	
4	acute	38.37±2.15	33.34±2.48	25.24±2.41
	reconvalescence	26.07±2.63	34.05±2.35	
TNF-α	acute	58.32±4.61	48.11±2.39	23.88±2.31
	reconvalescence	27.92±3.98	37.62±2.18	

Conclusions

Thus, in children infected with herpesviruses, RVI in the debut of the disease in terms of the severity of clinical manifestations is inferior to that in children who do not have background infection. However, the duration of their presence is more significant. These features, apparently, are caused by the insufficiently pronounced reaction of proinflammatory interleukins in the blood of children infected with the herpes viruses at the onset of the disease and the preservation of their indicators at a relatively high level during the course of the disease.

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A LETHAL CASE OF VIRAL-BACTERIAL PNEUMONIA WITH RELATIVE LYMPHOPENIA: RETROSPECTIVE EVALUATION

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Abstract

The author presents a clinical case of a fatal course of community acquired viral-bacterial pneumonia in a patient without underlying risk factors but with atypical course. Lymphopenia and neutropenia development is considered a prognostic factor for severe course and the probability of a fatal outcome. Morphology demonstrated impairment of vascular endothelial cells, hypoplasia of the lymphoid follicles in the spleen, massive necrosis of the liver parenchyma with hemorrhages. At present such case should be differentiated with pneumonia caused by mycoplasmas, legionella, rickettsias, chlamydia, pneumocystis, as well as, in the presence of epidemiological data, with influenza A (H1N1) California 2009, influenza H5N1, coronaviral infection (MERS-CoV), that is infections complicated with acute respiratory distress syndrome (ARDS). The mechanisms of neutropenia and lymphopenia development in viral lesions of the respiratory system require further inverstigation.

Keywords: *viral-bacterial community acquired pneumonia, parainfluenza, S. aureus, lymphopenia, morphology.*

Introduction

Due to the evolution of viruses in the respiratory group, a change in the clinical presentation of viral and viral-bacterial pneumonia is possible [1, 2]. In addition, there are some similarities in the mechanisms of lung damage in viral respiratory infections(H5N1 Flu, A (H1N1) California 2009 influenza, MERS-CoV), which may cause relatively high mortality rates [3–9]. Neutropenia, lymphopenia in viral and viral-bacterial lesions of the respiratory system are associated with a severe course and the possibility of death [10, 11]. The bacterial process caused by viral infection of the respiratory system and St. Aureus, may be fatal even in young people without major risk factors. [12, 13]

Case

A 38-year-old female patient was brought to the hospital by ambulance on the third day of the disease in severe condition and was immediately admitted to the intensive care unit with pronounced general weakness, blackening of the eyes, sore throat when swallowing, breathing, talking, and similar pains along the trachea, as well as aphonia. The disease started 3 days before with sore throat, hoarseness, runny nose, fever up to 39–40 °C. Antipyretic drugs did not relieve the condition, she lost consciousness twice. Her blood pressure measured at home was 60/40 mm. Hg. The ambulance doctor administered dexamethasone 1.0, strophanthin 1.0, glucose 200.0 4%, intravenous drip, cordiamine 2.0 intramuscularly after which the patient was hospitalized.

Life history. She had vegetative vascular disorders in the past. At the age of 2 she was operated on for volvulus. There was no history of allergy. She also had furunculosis, long-time diet, took nutritional supplements. She denied ever the use of illicit drugs.

Epidemiological history. The patient denied any contact with infectious patients. Seven days before the onset of the disease she came back from China.

On examination. The patient presented on day 3 of the disease. The general condition was

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severe. The patient was sluggish but conscious. On examination, the skin was pale, there was diffuse hyperemia of the soft palate, submandibular lymph nodes were slightly enlarged. There was aphonia. Auscultation of the lungs to the right downward from the angle of the scapula demonstrated shortened percussion sound, there was no wheezing, and breathing was weakened. Her body temperature was 37.6°, blood pressure was 70/40 mm Hg and her heart rate was 128 per minute. The heart sounds were muffled, rhythmic. The respiratory rate was 32 per 1 min. Liver +1.5 cm. Urination was not changed, meningeal signs were absent. Chest X-ray showed inhomogeneous infiltration of the lung tissue in the form of large-focal shadows, in places of confluence, mainly in basal regions on the right, excluding the apex. On day 5 the infiltration of lung tissue on the right became homogeneous, the dome of the diaphragm on the right was not differentiated, which indicated the presence of effusion in the right pleural cavity. Homogeneous intensive left infiltration appeared (Segment 6). The damage to lungs progresses rapidly. By the decision of the case cinference, the antibacterial therapy was changed.

Laboratory and instrumental studies. On admission elevated leukocyte count (10.2×10^9/L) was revealed. There is well known fact that the percentage of various types of leukocytes sometimes does not reflect their absolute number, therefore an assessment of their relative and absolute values (in μL) is required (*Table*).

Lymphopenia, as a rule, is associated with severe infectious [14, 15]. Due to severe leukopenia and the appearance of solitary blast cells in two blood tests, a hematologist consultant was invited to rule out blood disease. His conclusion was leukemoid reaction. Thrombocytopenia was observed on day 5 of the disease (170,000 in 1 μl). Prothrombin index was 65% on admission, and 65% on the day of death. On day 5 urea (12.5 mmol/l) and creatinine (0.14 mmol/l) content elevated. Total bilirubin was 47 mcm/l, Alanine aminotransferase (ALT) – 0.42 mmol/l.h, on the day of death ALT was 3.8 mmol/l.h. Immunofluorescent test of a smear from the nasopharynx revealed antigens of parainfluenza virus. On day 6, Candida, Staphylococcus aureus (sensitive to oxacillin, rifampicin, cyfran, cephalexin) were revealed. ELISA HIV test was negative. Bacteriological examination of the blood for sterility was negative. Ultrasound examination on day 11 showed that the liver was enlarged by 2.5 cm, echo parenchyma increased, spleen measured 11×4.7 cm, echo was slightly elevated. A conclusion of parenchymal reaction of the liver and spleen was drawn. Urinalysis showed density 1024, protein 0.16 g/l, 5–6 white blood cells in the field of vision, 2–3 hyaline cylinders, red blood cells 30–40 unchanged in the field of vision, 15–20 in the field of vision, small amount of mucus. Feces test demonstrated liquid consistency, 30–40 leukocytes in the field of vision, 2–3 red blood cells the field of vision, small amount of mucus.

Reaction of nondirect agglutination with antigens of Sh. Sonnei, Sh. Flexneri (1–5 serotype) was negative, with antigen of salmonella group D (1, 9, 12 serotype) was also negative. Her blood group was A (II), Rh negative. Bacterioscopy of thick drop of blood did not identify any bacteria. On admission T helpers level was 27% (reference range (RR) 35–69). T suppressors made 15% (RR 5–20). Total complement amounted 0.956 units (normal 1.0–1.1). The patient was twice consulted by a phthisiologist, tuberculosis was excluded. Three times she was examined by a cardiologist, a neuropathologist.

The patient was administered ampioks 1 gram IV 6 times a day, arbidol 0.2g 4 times a day orally, lincomycin 0.6g 3 times a day. From day 3 she received contrical 10,000 U, indomethacin, levofloxacin 500 mg 1 time a day IV from day 8 to day 11 of illness, rovamycin IV 1.5 million

Hematology laboratory data in the dynamics

Parameter	Date of examination							
	03-Mar	4-Mar	05-Mar	06-Mar	8-Mar	09-Mar	10-Mar	11-Mar
White cells (10^9/l)	10.2	1.5	16.8	13.8	42.5	27.8	113.0•	75.0•
Neutrophils (%)	29	41	59	41	27	19	8	9
Lymphocytes (%)	48	18*	2*	4*	10*	4*	5*	5*
Lymphocytes absolute amount (ref. 1200–3000) in mcl	4896	270*	336*	552*	4250	1112*	5650	3750

Note. * – Lymphopenia • – Leukemoid blood reaction.

3 times a day, ceftriaxone 2 g 2 times a day IV from day 4 to day 11 of the disease. On day 4h artificial ventilation was administered; intubation was applied from day 8 of the disease to the death. Normal human immunoglobulin was administered IM 4 doses (6 ml) on day 4 of the disease. She constantly received high doses of 600 ml dopamine for 6 hours, 1200 ml for 6 hours of detoxification, dextrans, glucocorticosteroid (prednisone 90 mg per day). ECG showed sinus tachycardia, violation of repolarization, acute myocardiopathy.

Differential diagnosis. The rapid progression of the clinical signs required an early clinical differential diagnosis. It was necessary to exclude SARS, legionellosis, lung lesions in anthrax and plague. At present it is necessary to differentiate such clinical situations and avian influenza A (H5N1), A (H1N1) and Middle East respiratory syndrome (MERS – CoV). [16–18]. In the patient were forced to differentiate primarily SARS clinically, but with the help of an immunofluorescent test, parainfluenza was diagnosed and *S. aureus*, MSSA was isolated from sputum.

Auscultation did not reveal moist rales or crepitation, X-ray confirmed extensive pneumonia with an atypical character. The patient was admitted on day 3 of the disease and died on day 11. Another reason for differentiation is community-acquired pneumonia caused by methicillin-resistant staphylococcal strain and Panton-Valentine leukocidin (PVL) – producing *Staphylococcus aureus*. Necrotizing pneumonia due to PVL-positive *S. aureus* [19].

On admission the diagnosis of influenza, severe course, tracheobronchitis, bilateral pneumonia, septic shock was made.

Clinical diagnosis. Acute respiratory viral infection (tracheobronchitis, laryngitis), acute focal bilateral pneumonia right total left subtotal (from sputum bacteriologically was isolated *S. aureus*), severe course, grade 3 toxic shock, infection-toxic cardiomyopathy, pulmonary edema, grade 3 respiratory failure, swelling of the brain, secondary hypochromic anemia, DIC syndrome were diagnosed in the hospital.

Pathomorphologycal data. At autopsy, the mucous membrane of the larynx, bronchi, trachea were bluish, dull with greyish-yellowish overlays. The lungs were voluminous, dense throughout the lung tissue, the pleura was dull, greyish with dirty filamentous overlays. The tissue was motley, dark-red, with grayish pattern and brown sites. The spleen was enlarged, reddish on incision with moderate pulp scraping. Mediastinal lymph nodes were grayish on incision, mesenteric ones are enlarged and grayish. On microscopy, the alveoli contained serous exudate, solitary macrophages, desquamated cells of the alveolar epithelium, erythrocytes, solitary neutrophils, interalveolar septa were thickened due to proliferation of septal cells and infiltration with lymphoid cells. Liver hepatocytes were in a state of granular dystrophy, interstitial edema, a sharp plethora of capillaries of the sinuses, in places with hemorrhages per diapedesum. The brain had pronounced perivascular and pericellular swelling, plethora and paretic dilatation of blood vessels. Spleen microscopically is shown in Figure 6. There was hypoplasia (atrophy) of lymphoid follicles in the spleen, desolation of follicles. Thus, severe toxic damage of the vessels is noticeable: endothelial cells with picnotic nucleus, sometimes desquamation. The lungs have different size infiltration with neutrophils and apoptosis.

The presence of focal infiltration in the lung parenchyma with the destruction of lung tissue, presence of neutrophils and apoptotic bodies is determined. The beginning of formation of granulomatous tissue on its periphery.

Pathoanatomical diagnosis of bilateral serous-hemorrhagic pneumonia was made. On day 4 immunofluorescent test identified antigen of parainfluenza virus. There was swelling of the brain, trunk dislocation, incision, pronounced plethora of paretic vascular dilation, hemorrhages in the internal organs. Proteinaceous and fatty degeneration of parenchymal organs was recognized. The cause of death was intoxication.

Discussion. Today respiratory viruses threat to global health and cause epidemics and pandemics with significant morbidity and mortality [20]. Presumably, it was a variant of atypical viral-bacterial pneumonia [21, 22], but testing for atypical pathogens in our patient was not conducted. For parainfluenza the temperature does not rise to 39 degrees on the first day of illness. Auscultation did not reveal moist rales or crepitation, X-ray confirmed extensive pneumonia with an atypical character. Lymphopenia was not pronounced, including in absolute values, leukopenia, colitis syndrome, hypoplasia of the lymphoid follicles of the spleen were not characteristic for community acquired pneumonia due to parainfluenza virus and *Staphylococcus aureus*. The decrease in the number of T-lymphocytes indicates a deficiency of cellular immunity, namely insufficiency of cellular immunity. Despite the long-term study

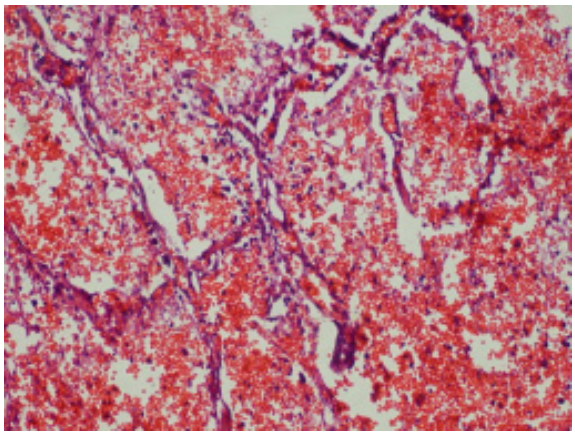

Fig. 1. Photomicrographs of lung tissue. ×400. Hematoxylin and eosin. The alveoli contain exudates with hemorrhagic component and a small number amount of macrophages, lymphocytes

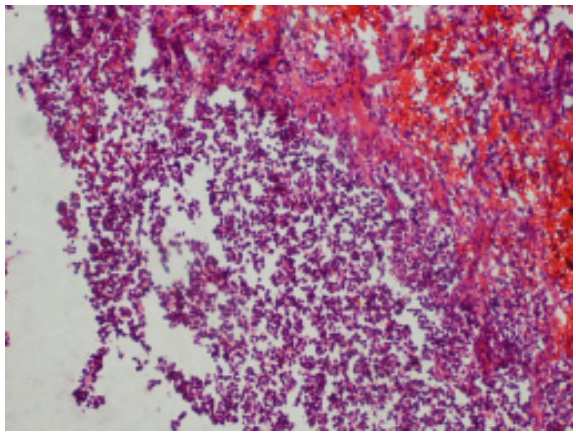

Fig. 2. Photomicrographs of lung tissue.×400. Hematoxylin and eosin

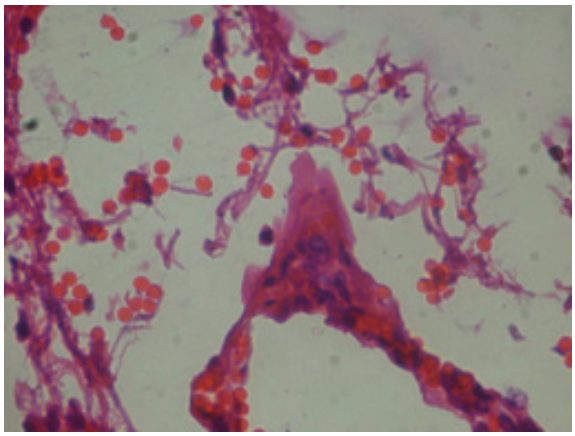

Fig. 3. Photomicrographs of lung tissue. ×400. Hematoxylin and eosin Plethora of capillaries of alveolar septa, red blood cells and sticks up to 20 microns long (Candida?) in the lumen of the alveoli

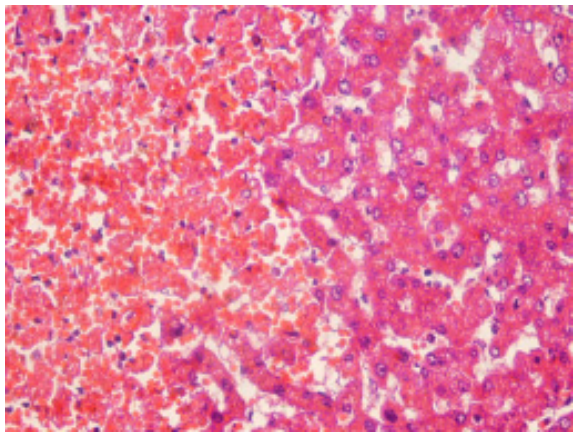

Fig. 4. Photomicrographs of liver tissue. ×400. Hematoxylin-eosin. Massive liver necrosis with hemorrhages

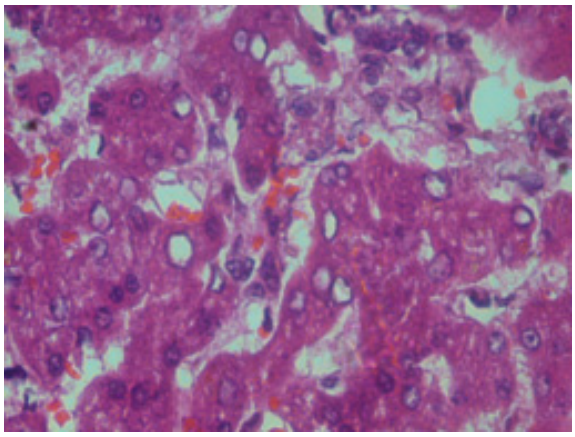

Fig. 5. Photomicrographs of liver tissue. ×400. Hematoxylin-eosin. Toxic damage to the liver. Polyploidy. Many hepatocytes have a nucleus with chromatin marginalization (apoptosis stage)

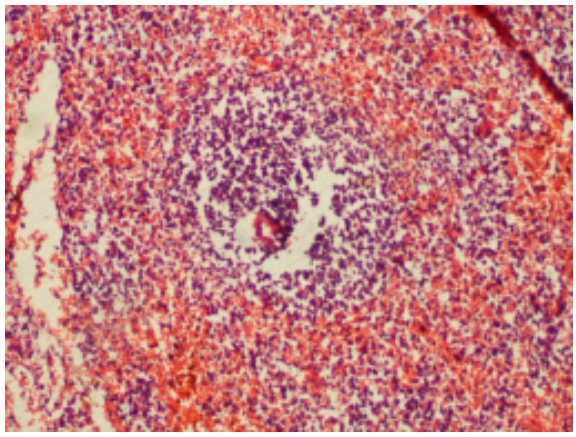

Fig. 6. Photomicrographs of spleen tissue. ×400. Hematoxylin and eosin-. Hypoplasia (atrophy) of lymphoid follicles in the spleen, desolation of follicles

of the pathogenesis of viral infections, its causes remain insufficiently studied. [23]. Cases of viral infection with the development of severe respiratory failure in the absence of a typical clinical picture of pneumonia may be associated with the threat of bioterrorism. It is also known that SARS pandemic was accompanied by high mortality. Atypical pneumonia can occur against a background of secondary immunodeficiency states. The mechanisms of neutropenia, lymphopenia are not clear enough. Perhaps their development is associated with the mechanisms of nonspecific immunosuppression. A feature of the pathogenesis of MERS-CoV, in which the virus infects the cells of the respiratory epithelium, causes changes in the regulation of cellular genes. It has been established that 207 genes in lung cells under the action of the virus are deregulated [24].

We are forced to make a retrospective assessment of fatal clinical cases of viral-bacterial pneumonia due to the emergence of new features of pathogens, which leads to changes in certain parts of the pathogenesis and clinical presentation of pneumonia.

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FEATURES OF THE CLINICAL PICTURE OF DEPRESSIVE DISORDERS OF DIFFERENT REGISTERS IN UNIVERSITY STUDENTS

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Abstract

In the course of work with the purpose of developing a complex pathopsychologically grounded system of psychotherapy and psychoprophylaxis for students of higher educational institutions with depressive disorders of affective (DDAR) and neurotic (DDNR) registers, a complex psychodiagnostic, psychometric, and clinical and psychopathological study of 200 students from various universities at the age of 17–24 was conducted.

According to the results of the study, it was revealed that the effect of factors related to the start of studies at the university results in the highest probability of depressive disorders of the neurotic register among younger students. Students of senior years are maximally adapted to the conditions of study; therefore, the incidence of these disorders, both clinical and subclinical, is average among them, whereas in senior years there is an increase in the incidence of depressive disorders of the affective register.

The article also presents the diagnostic results of studying the emotional sphere of students, the syndromological structure of depressive disorders of both registers, and formulated recommendations on the diagnosis and treatment of patients with depressions in the primary medical system.

Keywords: *depressive reactions, diagnosis, primary care, students, treatment.*

Introduction

Today's world has a tendency for acceleration of the pace of life, an increase in the number of communication links, intensification of social and economic tensions in society and urbanization. This leads to an increase in the prevalence of mental and psychosomatic diseases, above all borderline, neurotic level, putting forward the task of their early diagnosis, correction and prevention as a priority [1–3].

At the present stage of development of society general medical problems including the affective conditions, especially anxiety and depressive disorders, are particularly pressing. According to the WHO, currently more than 110 million people in the world – 3–6% of the population – have clinically significant manifestations of these disorders. A similar trend is observed in Ukraine [4–7].

The growing urgency of the problem of depression is due to their incidence, the significant influence of the disease on the quality of life and social functioning of a person, as well as the largest level of suicides among mental disorders [4, 8, 9]. All this leads to social disadvantages and economic losses [10, 11].

At the same time, the growth of depressive disorders does not occur due to endogenous forms, but due to psychogenic, reactive, mixed forms, which are called masked forms, somatogenic and which are manifested above all, as somato-vegetative disorders.

According to the World Health Organization (WHO), by the beginning of the 21st century, the proportion of depression and anxiety disorders was about 40% in the overall structure of mental illness, which is registered in the world. Every year about 200 million people in the world suffer from clinically diagnosed depression and this

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figure is steadily increasing. Every eighth person needs specialized antidepressant therapy at least once in his life [4, 12, 13, 5].

Particularly relevant, this problem occurs in relation to persons who are in conditions of prolonged or intense information stress, in particular, students of higher educational establishments (HEEs). Education in higher and secondary specialized educational institutions can be attributed to a specific type of activity, which is characterized by constant growth and complication of information, lack of time, increased requirements for solving problem situations, control rigidity and other factors [14–17].

2. Purposes, subjects and methods:

2.1. Purpose – basing on studying the structure and time course of depressive disorders of affective and neurotic registers in students of higher educational institutions, to develop a comprehensive pathopsychologically grounded system of their psychotherapy and psychoprophylaxis.

The object of study: depressive disorders of affective and neurotic registers in university students.

2.2. Subjects & Methods

The research was carried out from 2010 to 2013 in four stages. In the first stage of the study, 200 patients with depressive disorders of the neurotic and affective registers were investigated under informed consent with observance of the principles of bioethics and deontology on the basis of Kharkiv City Psychoneurological Dispensary No.3 and the Students' Youth Center for Mental Health in Kharkiv City Student Hospital (79 patients with depressive disorders of the affective register (DDAR) and 121 patients with depressive disorders of the neurotic register (DDNR)). In the second stage, on the basis of analysis of clinical features of emotional disorders and psychological properties of students, we determined the targets of their psychotherapeutic influence. Patients of the study group (SG), along with treatment in accordance with the standards of medical care for this disease received standard treatment and participated in implementation of measures of the psychotherapeutic correction system, developed by the author; control group patients (CG) received only standard treatment.

At the third and fourth stages of the study, active and supportive psychotherapy of students with depressive disorders of various genesis and an assessment of its effectiveness was conducted.

In this work a set of research methods was used, which included anamnestic, socio-demographic, clinical-psychopathological, psychodiagnostic and mathematical-statistical methods.

The anamnestic method was used to identify the anamnestic factors in the development of depressive disorders in the affective or neurotic register; the peculiarities of personality development and education in the family were studied.

The socio-demographic method involved the study of characteristics such as distribution of patients by age, level of education, family status, social status, university profile and type of work.

Clinico-psychopathological method was based on generally accepted approaches to psychiatric examination by interviewing and observing. The survey was conducted using diagnostic and research criteria of ICD-10. the standard psychometric self-assessing Beck Depression Inventory was used to assess the time course of mental state during the treatment and catamnestic observation [18]. The clinical-psychopathological method was supplemented by a survey using the individual card of examination of patients with depressive disorders proposed by us.

Moreover, psychometric study included the study of the severity of psychopathological symptoms using Hamilton Rating Scale for anxiety and depression (HDRS and HARS, 1960) [19] and Montgomery-Asberg Depression Rating Scale (MADRS, 1979). [20] Psychodiagnostic survey included the study of personal characteristics of students with the help of the Eysenck Personality Inventory (EPI) [21] and the diagnostic Buss-Durkee Inventory Questionnaire of Aggression (1957). [22]

Statistical data were processed using mathematical t-test method [23]. The method was to conduct a comparative study on the t-criterion according to the traditional method for parametric statistics. Also, the data were processed using t-test to determine the probability of disagreement between the groups [23].

Conflict of interests. There is no conflict of interests.

3. Results and discussion

Various studies conducted by scientists in Canada and collected in "Teaching students with mental health disorders: resources for teachers" [24] have shown, that adolescents with depression are commonly found to have sustained sadness and tearfulness. They cry easily and the sadness seems out of proportion to the apparent source of sadness. They are difficult to console. This

sadness can be quite frightening to young people with depression, who cannot seem to return to equilibrium easily and for whom the feelings seem overwhelming and endless. With younger ones this sadness more often takes the form of lethargy and listlessness. Unexplained irritation is a prominent symptom of depression in students of all ages. They are quarrelsome, disrespectful of authority, hostile and prone to sudden anger. There is increased shouting and screaming. Students are seen as agitated, which is demonstrated by the inability to sit still, excessive fidgeting, picking or pulling at hair, skin, clothing or other objects. Alternatively, there may be some psychomotor retardation - coordination is poor and the studen looks clumsy. Students with depression may withdraw from participation in different activities, have difficulty concentrating and making decisions. Loss of energy, easily and quick annoyance and hypersensitive to the comments and actions of others, sleep disturbances and substance abuse are very common to this contingent.

Another research [25] showed that the strongest population-level baseline predictors for major depressive disorder (MDD) in first-year college students were history of childhood-adolescent trauma, stressful experience in the past 12 months, parental psychopathology, and other 12-month mental disorder.

The results of the study of medical students show an increase in anxiety-depressive symptoms in fifth-year-students relative to the first one almost doubled. [26, 27]

Research results. Our clinical analysis showed that emotional disorders in patients of the study group were most often structured in the form of such manifestations of emotional disorders as: depressive disorders of the affective register, depressive episode in 52.8%±5.6 and recurrent depressive disorder in 36.1%±5.4 cases. In depressive disorders of the neurotic register, adjustment disorders were found in 55.6%±4.5 and prolonged depressive reaction in 35.8%±4.4 cases.

The results of the study showed that the number of students assigned to certain observation group depended on their gender and year of study. The depressive disorder of the affective and neurotic registers often affected females (67.1% with DDAR and 60.3% with DDNR, at $p< 0.05$). Depressive disorder of the affective register was more common among students of the fourth (26.6%) and fifth (59.5%) years of study. While depressive disorder of the neurotic register was significantly prevalent among first-year (43.8%) and second-year (38.8%) students (at $p<0.01$).

The time course of mental state of students throughout the course of study is characterized by a wave-like course. The greatest number of complaints of general character and symptoms in different psychic spheres was observed in the students of the first two years. Subsequently, they gradual declined and only in the senior years this indicator rose again. The results of our study showed that there were general patterns of the time course of mental state of students that did not depend on the profile of the university and the duration of the training, but only related to its periods (junior, middle and senior years). Probably, this fact can be explained by the effect of the adaptive mechanisms to the conditions of learning, which determine the number and combination of complaints and symptoms in different mental areas.

Thus, in depressive disorders of the neurotic register, deterioration of general well-being was first of all determined by a decrease in mental working capacity, quality of night sleep, presence of headaches (51,2%), and somatovegetative disorders. Most students presented with inattention (91.7%), fatigue (90.0%), mental tiredness (69.4%). Dissomnic symptoms were manifested in the form of violations of the duration and quality of night sleep, increased drowsiness, difficulty falling asleep, lack of vivacity after sleep (92.6%).

Among various disorders of perception, hyperesthesia was most often found (66.2% of students) against the background of intense learning activity. It, in turn, could be accompanied by emotional distraction, irritability (87.6%).

In the structure of thought disorders, two main groups of symptoms were identified: disorders associated with learning activities, and negative thoughts about their own personality or relatives. The most frequent symptoms of the first group include the difficulty of understanding the contents of what was read or heard (54.5% of students) and a decrease in wit (35.2%). The second group of symptoms was represented primarily by concerns about health (71.2%), disability and low value (67.6%), thoughts about the problems in family and loved ones (76.1%).

Emotional disorders were most often represented by a rapid change in mood (100.0% of students), irritability (87.6%), anxiety, feeling of inner tension (75.2%), and a decline in the range of interests (46.3%), indifference to one's condition and one's fate (31.6%), coldness, and

sometimes hostility to close ones (71.6%). These symptoms were more common during the exam sessions, especially in junior students.

The incidence of effector-volitional disorders was as follows: isolation (83.2% of students), lack of activity (66.2%), lethargy, inactivity (61.3%), or increased activity with rapid fatigue (69.4%), self-doubts (85.8%). The presented symptoms also intensified at the end of the semester and often continued at the beginning of the vacation period.

Vegetative disorders, first of all, included vegetative-vascular impairments, including face reddening in excitement and rest states (56.8%), increased blood pressure (46.3%), tachycardia (79.3%), and sweating (67.8%), tremor of fingers and hands, especially under emotional stress (62, 7%).

In case of depressive disorders of the affective register, basing on the conducted research, it was established that there were common psychopathological features of endogenous depressions of adolescence. First, they included pronounced polymorphism of presentation with incompleteness, fragmentary, variability of psychopathological symptoms and fuzzy registration of the affective triad. The analysis showed that the features of depressive states in the patients under investigation and their peculiarities should be explained by the significant contribution of pubertal psychosocial factors in their formation. This leads to the development of cognitive, behavioral and somatovegetative disorders typical for adolescents, not only masking their depressive basis, but also complicating the correct interpretation of individual symptoms of the disease.

Thus, the detailed analysis of the structure of juvenile depressive states showed that only in 15.3% of patients the presentation approached the typical melancholy depression characteristic for mature patients, but still, differing from the latter by the lack of a harmoniously presented "classical" depressive triad.

In the structure of the depressive syndrome of affective register, first of all, attention is paid to the insignificant severity of the actual thymic component. As a rule, patients experienced a decline in vital tone, and the main plot of their experiences was the feeling of rapid "mental exhaustion", "inattention", "moral impotence", "moral indifference" (complaints of weakness in 89.9%, fatigue in 91.1%, apathy in 77.2%, loss of ability to work in 74.7% of the examined). The manifestations of such ideational disorders usually prevailed over the typical signs of depressive syndrome. In addition, some patients expressed the idea of self-exclusion (94.9%), inferiority, suicidal thoughts, accompanied by a predominance of vegetative and visceral crises, somatic-autonomic disorders of the cardiovascular and respiratory system (fluctuations of blood pressure in 35.42%, difficulty breathing in 40.5%, rapid heartbeat in 11.4%, increased sweating in 8.9% of the examined students). Youth depression was manifested by fussiness, accelerated speech, up to motor stimulation and agitation. At the same time, anxiety in 87.3% of patients was felt physically (in the chest, head), which allowed to talk about its vital nature. In addition, some of the patients observed daily oscillations with the most pronounced anxiety in the second half of the day. Vital disorders in students were often expressed by decreased "vital tone", "lack of energy" or a sense of emotional discomfort. In a number of cases this was evidenced by the ideas of inferiority, gloomy assessment of the future, domination of memories of sad and unpleasant events (46.8%), pessimistic reflections on the lack of purpose of human existence, eventually formulated in a system of metaphysical, overvalued depressed world outlook.

It is necessary to pay special attention to the features of ideational disorders in patients with juvenile depressions of the affective register occupying the dominant position in the clinical picture in most of them. These disorders of different qualitative structure were found in almost all patients. Along with this complex of symptoms, patients suffered from impaired memory and attention (in 63.3%), which also indicated retardation of intellectual processes. Clinical and psychopathological investigation allowed to determine the prevalence and syndromological structure of mental disorders in the examined patients of both groups. Thus, in patients with DDAR, the presence of asthenia-depressive syndrome was detected in 83.5%, anxiety-depressive in 87.3%, and somatic and vegetative syndrome in 27.8% of the subjects. The presence of asthenia-depressive syndrome in 97.5% of cases, depression-hypochondria syndrome in 60.3% of cases, and somatic and vegetative syndrome in 52.1% of cases was observed among students with DDNR.

The conducted study showed that on the Hamilton scale, in the majority of patients with DDAR in SG1, moderate anxiety prevailed (20.6±2.3 in 37.5% at $p<0.01$) and depression of moderate and severe degree (21.1±2.2 in 37.5% and 32.4±1.9 in 50.0% respectively at $p<0.01$).

There were no reliable differences in indicators in SG1 with indicators in CG1.

In the majority of the subjects from the SG 2, patients with DDNR, reliably presented with manifestations of anxiety (15.5±1.1 in 41.98% and 20.7±2.2 in 28.4% surveyed at $p<0.01$), an indicator of mild and moderate anxiety and depression (21.7±2.3 in 40.7% , a credible predominance of moderate depression at $p<0.01$). There were no reliable differences between indicators in SG2 and indicators in CG2.

Assessment by the Montgomery-Asberg Depression Rating Scale of students with DDAR in SG1 showed a significant prevalence of depressive episode: minor - 20.7±2.8 in 22.9%, moderate - 28.1±1.3 in 27.1% and major - 36.7±1.02 in 39.6% at $p<0.01$. Students with DBNR had a significant prevalence of minor (21.4±1.9 in 56.8%) and moderate (27.9±1.4 in 22.2%) depressive episodes in SG2 at $p<0.01$. There were no reliable differences between indicators in SG1 and indicators in CG1 and SG2 with CG2.

According to Beck Depression Inventory, most students with DDAR noted the presence of moderate depression (25.4±2.3 in 37.5%) and severe (34.7±1.9 in 31.25%) depression in SG1 at $p<0.01$. Most students with DDNR noted the presence of mild (12.1±1.5 in 32.1%) and moderate (17.8±1.1 in 27.2 %) depression in SG2 at $p<0.01$. There were no reliable differences between the indicators in SG1 with indicators in CG1 and SG2 with CG2.

According to different researches [28], depressive personality and some traits, particularly neuroticism/negative emotionality, predict the subsequent onset of depressive disorders. However, it is unclear at this point whether they are best conceptualized as precursors or predispositions, as it is difficult to differentiate between these models, and there is evidence supporting both accounts. In either case, there is growing evidence that temperamental risk factors are evident at an early age, suggesting a promising approach to identifying young children at risk for depression.

In our work we found, that the general assessment of indicators on the scales of neuroticism and extraversion / introversion of the Eysenck Personality Inventory allowed to conduct an analysis of the types of temperament in the students under investigation. Relatively predominant type of temperament in the group of patients with depressive disorders of the neurotic register was choleric (in 42.1%), sanguine type was found less frequently, namely in 9.9 % cases, than phlegmatic (in 32.2%) and melancholic (in 15.7%) due to high rates of extraversion in most of the students under study.

Most students with depressive disorders of the affective register predominantly had phlegmatic type of temperament (in 59.5 %), the least common was sanguine (in 6.37% surveyed) type due to high rates of introversion.

Literature review showed that the correlation between aggression and depression is not important enough to become a powerful predictor of either close or remote event. This means that, despite the existence of a specific association, it is too weak and, in fact, in the literature it appears as a variable association [29]. The fact that the correlation between anger and depression is weaker than the correlation with aggression is something that appears in the literature repeatedly [30]. It becomes apparent that for the purpose of emotional interaction, anger trait represents a more important role than the anger state which we can find consistently in previous research about emotions in adolescence [31]. This is perfectly coherent given that anger state is crucial and it is not permanent and therefore it has to vary much more easily than anger trait [31, 32].

To sum up the literature review, in the models it becomes apparent that instability predicts depression and anger, but not aggression, the latter only appears if instability is associated to anger. The prediction of emotions of the internalized kind can predict those internalized directly, but also the indirectly internalized if we take anger into account. It is obvious that all this has consequences in the preparation of all programs for the establishment of emotional control over adolescents, as it is necessary to take into account as the direct aim not only the control over externalized emotions such as anger, but also over internalized emotions such as emotional instability [33].

When analyzing the indicators by the Buss-Durkee Inventory questionnaire of aggression in our research, particular attention was paid to the scales of physical aggression and irritability. They together form the index of aggression (both direct and motivational), and also on the scale of images and suspicions, which are components of the index of hostility.

The Buss-Durkee Inventory questionnaire showed links of indicators of aggression and hostility with violations of socio-psychological functioning in the sphere of interpersonal duties,

communication, and sexual relationships. A number of patients in this group in the premorbid stage were found to have active, extrapunitive forms of aggression and hostility (in the form of suspicion), as well as intrapunitive forms demonstrated as suicidal tendencies and self-destructive actions.

High rates of hostility and anger were informative indications, which reliably indicated depressive episodes already existing in the history and the belonging of the group under study to the "high risk of becoming depressed". These students also demonstrated special coping strategies in the form of a tendency to "blame themselves in negative events", "blame others", and "seek social support". The combination of these factors – intense anger, high hostility, a tendency to accusations to their own address and the address of other people, the influx of thoughts of negative content, create "interpersonal storms", impede the reception of the desired support and dramatically increase the likelihood of manifestation of depression.

Based on the obtained results, we have substantiated and developed an algorithm for providing psychotherapy for students with depressive disorders of affective and neurotic registers.

For the solution of the tasks, drug (new generation antidepressants - selective serotonin reuptake inhibitors (SSRI)) and non-drug (Cognitive Behavioral Therapy (CBT) in the modification of A. Beck) methods were used. The control group simultaneously received standard drug therapy (antidepressants).

Psychotherapy was carried out simultaneously with administration of drugs and was conducted in three stages.

Task of the first (didactic) stage: awareness of the mechanisms of disease development and therapy.

Task of the second (actually cognitive) stage: detection of maladaptive "automatic" thoughts that support disappointment, depression, negative self-perception.

Task of the third (behavioral) stage: a special strategy that teaches self-esteem and forms positive motivation.

Psychotherapeutic techniques in students in study groups had different emphasis on intervention. So, CBT in DDAR was aimed at eliminating the motivational, behavioral and physical symptoms of depression. The patient was helped to restore the ability to control the situation, cope with it, overcome the feeling of incompetence and helplessness, overestimate the usual life difficulties that were perceived as unbearable, overcome fatigue and inertia. An important role in the recovery was played by the refutation of negative expectations and demonstration of motor ability.

CBT in DDNR was aimed at understanding the role of stress that arose in the development of a patient's illness. The necessary stage of work was the change in the attitude of the patient to the traumatic (stress) situation and its adoption as part of life experience. An important part was the reassessment of their own role in a traumatic situation, the assumption of a certain share of responsibility with the formation of an active position in overcoming the current circumstances.

After the period of formation of compliant relations, 14–16 sessions of CBT were conducted within two months. Students with pronounced somato-vegetative components were trained in the technique of autotraining (AT) in the modification of B.V. Mykhaylov [34].

In summary, the study of the effectiveness of the conducted program of psychotherapy in the study groups, compared with the control groups, was assessed by objective (Montgomery-Asberg Depression Rating Scale (MADRS)), and subjective criteria (Beck Depression Inventory).

The effectiveness of the treatment in RG1 was 67.23%.

The effectiveness of the treatment in RG2 was 88.58%.

Thus, the application of our model of psychotherapy, built on the integrative principle, has shown its high efficiency. Owing to the integrated approach in the treatment of depression disorder among university students after the completion of the course of psychotherapeutic activities, there was an increase in the level of motivation and interest in learning, as well as further employment. Students found improvement in the cognitive field, which was manifested by increased attention concentration, memory improvement and resistance to stressors. The effectiveness of the proposed model was 77.9%.

Conclusions:

1. Diagnosis of depressive disorders should involve psycho-diagnostic data of psycho-emotional state analysis and take into account syndromological structure of depressive disorders of the affective or neurotic register to normalize the state of the emotional sphere in students with depressive disorders of both registers.

2. The program of psychotherapy should be built on an integrative principle, combining a

systematically stratified step-by-step approach and taking into account the individual-typological features of patients.

3. This three-stage psychotherapy program should be used in practice (awareness of the mechanisms of disease development and therapy; identification of maladaptive "automatic" thoughts, self-esteem training and the formation of positive motivation; as well as auto-training techniques) for students of higher educational institutions who suffer from depressive disorders due to its high effectiveness in primary medical care.

4. In order to implement the psychotherapy system, it is necessary to involve psychiatrists and psychotherapists in the specialized unit of the institutions providing primary medical care.

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