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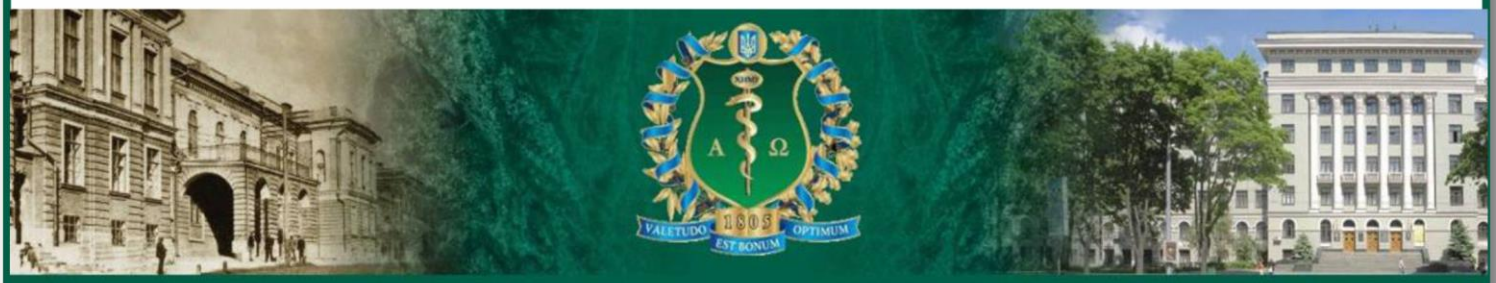

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PROBLEM LECTURE

Ashcheulova T.V., Kochubiei O.A., Ovrakh T.G.*

PREVENTIVE CARDIOLOGY, PRECLINICAL DIAGNOSES: OLD PROBLEMS – NEW APPROACHES

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Abstract: The article discusses the new Guidelines on cardiovascular disease prevention in clinical practice (2016) which summarized novel approaches of detection of such risk factors as overweight, obesity, abdominal obesity, smoking, dyslipidemia (cholesterolemia, triglyceridemia), blood pressure (BP) levels, glucose, insulin, insulin resistance, inflammatory markers, such as c-reactive protein, which can be widely used in practice.

KeyWords: Cardiovascular disease, preventive cardiology, risk assessment and stratification, strategy for prevention of cardiovascular diseases.

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality all over the world. The current strategy for their prevention and treatment considers the pathophysiological mechanisms of the impact of risk factors, as their early detection and correction can result in a significant improvement of cardiovascular prosthesis [1].

Therefore, it is very important to find out early markers of cardiometabolic disorders which can help to identify persons with risk of obesity, type 2 diabetes mellitus (DM2T) on preclinical level. Prevention of CVD is one of the highest priorities, because two thirds of the risk factors are caused by the way of life, which includes a variety of psychosocial stressful life events, chronic stress at work, lack of social support, low socio-economic status, tensions of family relationships, and so on.

In 1994 the European Society of Cardiologists developed and published the guidelines for the prevention of ischemic heart disease in clinical practice [2]. In 1998, the Joint Expert Group published their review, proposing the requirements to the way of life, highlighting the influence of risk factors and identifying therapeutic target points for prevention.

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The second edition, which was supplemented and approved by the European Society of General Practice and the International Society of Preventive Medicine, provided a lot of new data that became the basis for their next revision [3]. In 2007 (updated by the European Stroke Organization) lifestyle counseling received much attention, and the approach to the assessment of cardiovascular risk using a scale of relative risk was changed [4].

In April 2016 European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice published Guidelines on cardiovascular disease prevention in clinical practice. These Guidelines summarized novel approaches concerning the detection of such risk factors as overweight, obesity, abdominal obesity, smoking, dyslipidemia (cholesterolemia, triglyceridemia), blood pressure (BP) levels, glucose, insulin, insulin resistance, inflammatory markers, such as c-reactive protein, which can be widely used in practice [5].

The new Guidelines stipulate that the level of CVD mortality can be decreased by half due to a rather moderate reduction of risk factors. CVD prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimizing the impact of CVDs and related disabilities [5]. The new Guidelines on cardiovascular disease prevention in clinical practice recommends to assess total CVD risk in an individual along with prevention of CVD: the higher the risk, the more intense the action should be.

The updated recommendations consider risk assessment and stratification to be an important prerequisite for successful CVD prevention. Individuals with low risk are recommended to maintain proper lifestyle as long as possible (ideally during lifetime); those with increased risk need correction, and the higher the risk is, the more correction they need, and the higher the original risk is, the more benefit they will have from correction measures.

The increase in the number of CVD promotes the relevance of programs for their prevention, control and monitoring of risk factors distribution. According to the WHO the strategy for prevention of diseases can be developed for masses (measures at the level of legislation, lifestyle changes), and for people with high risk (aimed at groups of people with a high risk of certain diseases) [6]. The combination of these strategies is supposed to be optimal.

Primary prevention includes a range of medical and nonmedical interventions aimed at prevention of deviations in health condition and diseases common to the entire population of selected regional, social, age, professional and other groups. Secondary prevention involves a complex of medical, social, hygienic, psychological and other measures aimed at early detection and prevention of exacerbations, complications, and chronicity of illnesses, and disabilities that cause maladjustment of patients in society, as well as reduced abilities, including incapacitation and untimely death.

Patients with CVD have a high risk of developing cardiovascular complications. They require more intensive changes of lifestyle and, if necessary, prescription of drug therapy. Relatively healthy "asymptomatic" patients need preventive measures in accordance with their level of risk. There have been proposed various models to determine the risk of CVD development in "asymptomatic" patients, which use multivariate analysis of different combinations of risk factors in populations. In particular, in Western European populations the prevalence of coronary heart disease among working population is lower in comparison with Eastern Europe, and mortality from fatal cases is two times lower. It is quite obvious that campaign against hypertension is not only necessary, but also possible. These trends in developed countries are due to preventive health care and, in particular, development of "Recommendations for prevention of cardiovascular diseases in clinical practice."

Clinicians should assess the general risk of CVD to intensify the preventive measures such as introduction of diet recommendations, individualization of extension of physical activity, and, if necessary, prescription of drug therapy with the use of drug doses or their combinations, ensuring control of risk factors. Recommendations should not be based on the analysis of any of the risk factors separately. To determine relative personal risk, the obtained results are compared with the parameters of non-smokers of the same age and sex, with AD less than 140/90 mmHg and cholesterol level below 5 mmol/l (190 mg/dl).

Consequently, to maintain low risk or to decrease it, patients must stick to the following guidelines:

1) complete refusal from smoking;
2) healthy diet;
3) sufficient physical activity;
4) body mass index <25 kg/m2, absence of central obesity;
5) blood pressure <140/90 mm Hg;
6) the level of cholesterol <5 mmol/l (190 mg/dl);
7) low-density lipoprotein cholesterol (LDLC) < 3 mmol/l (115 mg/dl);
8) concentration of blood glucose <6 mmol/l (110 mg/dl).

At the same time, people at high risk of cardiovascular diseases are recommended to control a number of parameters:

1) BP <130/80 mm Hg, if possible;
2) Total cholesterol <4.5 mmol/l (175 mg/dl); if possible – <4 mmol/l (155 mg/dl);
3) LDL cholesterol <2.5 mmol/l (100 mg/DL); if possible, <2 mmol/l (80 mg/DL);
4) Blood glucose <6 mmol/l (mg/DL) and HbA1c <6.5 percent, if possible.

Thus, a strategy for individuals at high risk must be complemented by public health measures to encourage a healthy lifestyle and to reduce population levels of CV risk factors.

Smoking cessation strategy includes 5A [5]:

1A – ask: systematic identification of smokers;

2A – assess: assessment of readiness to stop smoking;

3A – advise: convincing advice to stop smoking;

4A – assist: recommendation of nicotine replacement therapy;

5A – arrange: organization of schedule of visits.

The strategy of making healthy food choices. Healthy diet is an integral part of the control of risk factors. Each case requires professional advice on the choice of the diet, which minimizes the risk of CVD, promotes the normalization of weight, blood pressure, lipid metabolism, controls blood glucose levels, reduces the risk of thrombosis.

The strategy of physical activity increase. Physical activity should be promoted in all age groups, both among adults and children. A special attention should be paid to the risk group in which increased physical activity should lead to a reduction in the risk of CVD. The goal to strive for is physical activity for at least half an hour daily, although more moderate activity is also useful.

The strategy against overweight and obesity. Prevention of excess weight gain or reduction is important for patients with CVD, and for those who have a high risk of CVD. Weight reduction is highly indicated to obese patients (body mass index (BMI) more than 30 kg/m2), overweight patients (BMI – 25-30 kg/m2), and those with abdominal type of obesity (waist circumference more than 102 cm in men and 88 cm in women). Success in weight reduction is supposed to be more appreciable if it is supported by professional physicians, on the one hand, and presence of motivation in patients, on the other.

The strategy of lipid content control in blood plasma. In general, the level of cholesterol in blood plasma should not exceed 5 mmol/l (190 mg/dl), and LDLC – 3 mmol/l (115 mg/dl). For patients with clinically determined CVD and for people with diabetes the target levels of cholesterol should be below 4.5 mmol/l (175 mg/dl) and LDL cholesterol – below 2.5 mmol/l (100 mg/dl).

The strategy of achieving the optimal level of blood pressure. The risk of developing CVD is continuously growing with the increase in blood pressure, once it exceeded the normal range. The decision to start therapy depends not only on the BP level but also on the degree of total cardiovascular risk and presence or absence of target organ damage. In patients with determined CVD, the choice of antihypertensive therapy depends on the underlying cardiovascular pathology. Drug therapy should be immediately initiated in patients with systolic BP 180 mm Hg or diastolic blood pressure 110 mm Hg and above regardless of their total cardiovascular risk.

Behavior risk factors. The lifestyle change is required for the majority of patients with determined CVD and high risk of its development.

The need for prevention of CVD in Ukraine is specified in the documents and regulations, but it is rather declarative. The successful implementation of CVD prevention guidelines relies heavily on general practitioners providing risk factor evaluation, intervention and patient education.

CONFLICT OF INTERESTS

There is no conflict of interests.

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PEDIATRICS

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CLINICAL MASKS OF ACUTE LEUKEMIA IN CHILDREN

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Abstract: For the study of initial clinical signs of acute leukemia in children 92 case histories have been analyzed. Among them acute lymphoblastic leukemia was in 81.5% of cases and acute myeloid leukemia was in 18.5% of cases. In most children the disease manifested with intoxication (94.6 ± 2,3%), lymphadenopathy (84,8±4,7%), hepatosplenomegaly (96,7±2,3%), anemic (82,6±4,9%), haemorrhagic (77,2±5,4%) syndromes. However, only in half of the cases the correct diagnosis was established in period less than 2-3 weeks since the first symptoms appeared. Consequently, it is necessary to pay attention of general practitioners to the variety of non-specific initial symptoms of acute leukemia in children.

KeyWords: acute leukemia, children, diagnostics, clinical symptoms.

INTRODUCTION

Acute leukemia (AL) still remains to be one of the challenges in pediatric hematology due to increasing prevalence of the disease, severity, difficulties in early diagnosis of the disease. AL takes a leading place among cancers in children. According to the Bulletin of National Cancer Registry of Ukraine "Cancer in Ukraine" (2014-2015) [1] it is almost one third (29.3 %) of all cancer diseases in children with the incidence rate of 4.5 per 100,000 childhood population. Among them lymphoblastic forms constitute 80-90%. Modern capabilities of chemotherapy can achieve a high level of treatment and survival in patients with leukemia which is a potentially fatal disease. According to the Surveillance, Epidemiology and End Results (USA, 2016) [2] five-year survival rate of children with acute leukemia increased from 36.5% to 85.4% from 1975 to 2012. In Ukraine five-year survival rate is 75-80% in children with acute lymphoblastic leukemia, and it is 40-45% in those with acute myeloid leukemia.

However, variable initial signs of AL can complicate diagnosis at early stages. As a result it leads to late start of treatment.

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2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of the research was to study the initial clinical manifestations of acute leukemia in children and to improve methods of early diagnosis for timely start of therapy.

2.2 Subjects & Methods

The study involved the assessment of 92 case histories of children aged from 6 months to 18 years. All these children were treated at the hematology department of Kharkiv City Children's Clinical Hospital No.16 with diagnosis of acute lymphoblastic leukemia (81.5% of patients) and acute myeloid leukemia (18.5%). Among them were 58 boys and 34 girls.

AL diagnosis included morphological, immunophenotypical analysis of blast cells and cytogenetic analysis. Most patients (83.9%) with acute lymphoblastic leukemia (ALL) had B-lymphoblastic form. Among them 70.97% had B type, common ALL and 12.93% had pre-B ALL. T-lymphoblastic forms of ALL were diagnosed in 16.1% of children. Other patients had myeloid forms of AL. There were 6 children with M4 variant, 4 children with M1, 2 children with M0, 2 children with M2, 2 children with M5 and one child with M3 variant.

Treatment of patients was performed by BFM protocols (Berlin - Frankfurt - Munster) adapted for Ukraine. Children with newly diagnosed ALL were treated with standard

doses of drugs according to the program ALL IC-BFM -2009, and those with AML were treated according to AML-BFM - 98/2000 protocol.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Significant polymorphism and variability of symptoms in children and adolescents under investigation were typical for clinical manifestation of AL.

Among observed patients there were 34.2±5.4 % of girls and 65.8±5.4 % of boys. Analysis of the distribution of patients showed that boys had AL significantly (p=0.0004) more frequently (Tab. 1). The disease started at the age less than 8 years in 48.9±5.7% of cases. At the same time the most severe AL course was observed in boys at adolescence.

Table 1.
Distribution of AL patients by age at the moment of diagnosis

Statistical parameter	Total	Age, years		
		2-7	8-14	15-18
Absolute Number	92	45	36	11
p% ± Sp%	100	48.9± 5.7	39.2± 5.5	11.9± 3.5

Assessment of medical history showed that the diagnosis was most typically determined within the period of 2 weeks to 2 months on average since first clinical examination. More than half of lymphoblastic leukemia cases (52.0%) were diagnosed in the period of 2-3 weeks since the first signs. Myeloid leukemia was diagnosed in 2-3 months on average. In 15.4% of patients with leukemia diagnosis was not made for the whole year. In 53.9 ± 5.7% of cases there were errors in early diagnosis of acute leukemia. It was more commonly confused with infectious diseases (31.7 ± 7.2%), anemia (26.8 ± 6.9%) and thrombocytopenia (17.1 ± 5.8%). Less commonly initial diagnosis included lymphadenopathy (12.2 ± 5.1%) only instead of ALL, rheumatic diseases (4.9 ± 3.3%), Henoch-Schönlein purpura (4.9 ± 3.3%) and "acute abdomen" (2.4 ± 2.2%). All these mistakes in timely diagnosis resulted in later start of treatment. It is important to note that the four of the observed children were established to have another cancer disease. One of them had ALL, but he underwent surgical removal of a testicle due to the wrong diagnosis of low differentiated carcinoma of testicle. Another one underwent removal of the tumor in the forehead followed by the course of chemotherapy. The third child's disease began as aplastic anemia. And in one patient AML developed as a secondary disease after Hodgkin's disease with inadequate intensive course of chemotherapy and radiotherapy.

Initial clinical symptoms of AL in the majority of observed children were not specific, but their severity significantly determined further course and prognosis of the disease. At the onset of the disease the majority of patients had symptoms of intoxication (94.6 ± 2.3%), that were most evident in boys (p= 0.0000) regardless of the form of leukemia (Tab. 2).

Table 1.
Distribution of AL patients by age at the moment of diagnosis

Syndrome		Total p% ± Sp% (n=92)	ALL p% ± Sp% (n=75)	AML p% ± Sp% (n=17)
Fever		82.6 ± 4.8	81.3 ± 3.4	88.2 ± 7.3
Intoxication		94.6 ± 2.3	90.7 ± 3.7	94.1 ± 6.9
Pain syndrome	osteoarticular	47.8 ± 6.5	48.0 ± 4.2	47,0± 7,2
	abdominal	29.3 ±5.9	29.3 ± 5.6	29,4 ± 6,9
Hemorrhagic syndrome		77.2 ± 5.4	69.3 ± 5.8	88.2 ± 12.0
Hepatolienal syndrome		96.7 ± 2.3	97.3 ± 2.2	94.1 ± 6.9
Lymphadenopathy		84.8 ± 4.7	90.7 ± 3.7	52.9 ± 13.3
Leukocytosis		52.2 ± 6.5	53.3 ± 6.3	52.9 ± 13.3
Anemia		82.6 ± 4.9	89.3 ± 4.02	70.6 ± 12.0
Thrombocytopenia		81.5 ± 5.1	85.3 ± 4.4	94.1 ± 6.9
Increased level of acute phase proteins		90.2 ± 3.9	89.3 ± 3.5	94.1 ± 5.4

Fever was present in 82.6± 4.8% of cases and it was more typical for boys (p= 0.0231). At the time of hospital admission 23.7 ± 4.9% of children were found to have decreased physical development (one or more σ in height and weight) which was more typical in girls (38.5 ± 9.5% in girls

VS 16.0 ± 5.1% in boys; p =0.0172).

Pale skin was observed in almost half of the children (43.4% of children) without a significant difference between the groups. Swelling of the lower extremities, edema of eyelids was observed in small number of patients and it was likely associated with hypoproteinemia.

Ostioarticular pain was reported by 47.8 ± 6.5% of patients and in 23.7% of cases pain in the bones and spine was the main presentation at the onset of the disease, and it was most prevalent in girls (p=0.0045). Pains in the abdomen were observed in 15.3% of cases. A headache was present in 9 children. Cardiac pain was observed in 2 children of older age.

Hemorrhagic syndrome at the onset of the disease was observed in most patients (77.2 ± 5.4%) with a tendency to be more common in AML (p=0.0580) regardless of gender (p=0.0955). Petechiae and ecchymoses on the skin of the upper and lower extremities were detected in 77.2 ± 5.4% of cases. Enanthema on the soft palate was observed in 51.3 ± 5.7% of children. Bleeding of mucous membrane of the oral cavity and nose was less common (in 11.8 ± 3.7% of children).

Lymphoproliferative syndrome was present in most patients. Lymphadenopathy was detected in 84.8 ± 4.7% of children. It was more frequent at lymphoblastic types of AL (p =0.0003) and in boys (p=0.0041). Hepatosplenomegaly was noted in the majority of children (96.7 ± 2.3%), regardless of gender and type of leukemia. Gingival hyperplasia as lymphoproliferative syndrome was observed in 9 cases and enlargement of testes was observed in 6 boys.

Cardiac syndrome at the onset of the disease developed in more than a quarter of cases (26.1%). This syndrome manifested as cardiac pains (in adolescents), dyspnea, arrhythmias, and decreased ejection fraction (less than 60% according to ultrasonography of the heart). Renal syndrome such as changes in urinalysis as leukocyturia, microscopic hematuria, proteinuria, rarely casts in urine manifested in 14.5% of children. Bronchitis or pneumonia was observed in 13.2% of patients. At the onset of the disease intestinal disorders in the form of diarrhea were reported by 9.2% of patients.

At the onset of the disease anemia was a frequent laboratory sign, occurring in 82.6±4.9% of children under investigation. It was more common in girls (p=0.0303). Thrombocytopenia was more common in boys (p=0.0491). Leukocytosis was found in 52.2 ± 6.5 % of patients and it was more common in boys (p=0.044). Leukocytosis more than 200 * 109/l was present in 12.9% of cases. Leukopenia was in 23.7% of patients without noticeable differences in AL type.

Indices of acute phase of inflammation (seromucoid, glycoproteins) increased in all children with AL at the onset of the disease, regardless of age and gender. Hypoproteinemia less than 60 g/L developed in 28.9% of children. Significant differences in levels of crude protein in different groups was not detected.

Discussion

This study shows that early diagnosis (less than 2-3 weeks since the first symptoms) was made just in about half of cases. In our opinion, diagnostic mistakes were probably associated with both variable manifestations and lack of oncological alertness and lack of information awareness of all diagnostic details of AL in children at primary care stage.

Analysis of literature showed that these problems in early diagnosis of AL and other types of cancer for pediatricians and general practitioners are typical not only in our country. Basing on the data of a review made by Dang-Tan T, Franco EL [3] in the developed countries the period from first signs to the diagnosis ranges from 1 day to several months, most typically several weeks.

One of described reasons of diagnostic delay is a relatively low incidence of childhood cancer and other life-threatening conditions [4]. Feltbower R.G., Lewis I.J. et al. [5] note that primary care practitioner sometimes examines a child with a new case of cancer only once in 20 years. According to Danish national population-based study [6] diagnostic interval for a quarter of children with cancer is more than 3 months.

In spite of this, Riccio I, Marcarelli M.[7] showed that musculoskeletal problems in pediatric acute leukemia was observed in 22% of children, this variant of manifestation

most frequently results in diagnostic difficulties [8,9,10].

To understand better the problems in AL diagnosis in children faced by general practitioners, Rachel T Clarke, Caroline HD Jones, Christopher D Mitchell and Matthew J Thompson conducted a study in Southern England with a thorough assessment of 18 pediatric AL cases with diagnostic interval from 5 days to 6 months, including interviews of 18 mothers, 3 fathers and 9 doctors [11]. According to their findings main reasons of diagnostic delay included wrong variety and non-specify of initial symptoms, wrong interpretation of the symptoms by doctors or patient's parents, problems of parent–doctor interaction, a relatively short and defined list of signs in most descriptions of manifestation of childhood leukemia.

4 CONCLUSIONS

Our study showed that lymphoblastic AL is much more typical in children. Among them there is B-type with general prognosis and a rarer T-type with favorable prognosis. Myeloid AL (M0 and M5) with less favorable prognosis and requiring the use of more intensive chemotherapy protocols is a less common pathology. Acute leukemia is more common in boys.

Despite the fact that the disease in the majority of children manifested with intoxication (94.6±2.3%), lymphadenopathy (84.8 ± 4.7%), hepatosplenomegaly (96.7±2.3%), anemic (82.6±4.9%), haemorrhagic (77.2±5.4%) syndromes, only in half of the patients the correct diagnosis was established in the period less than 2-3 weeks since the first symptoms appeared.

In the presence of hemorrhagic syndrome, severe anemia, expressed enlargement of the lymph nodes children were brought under the supervision of a hematologist in time. In other cases, variable and non-specific initial manifestations of AL in children and general practitioners' and specialists' lack of oncologic awareness led to late diagnosis and delayed start of the treatment. All these facts could affect the overall prognosis of the disease.

In conclusion, it should be noted that thorough history taking and comprehensive assessment of clinical symptoms are crucial in the early diagnosis of acute leukemia in children. If a child has symptoms of intoxication, pale skin, lymphadenopathy, hepatosplenomegaly, fatigue, weakness, weight loss, bone pain without any reason, it is necessary to perform a complete blood count test and to monitor blood test parameters over time. It is also necessary to consult a hematologist, especially when the treatment of the disease does not bring any adequate therapeutic effect.

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PEDIATRICS

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SIGNS OF INFLAMATION IN THE AIRWAYS IN CHILDREN WITH EXERCISE-INDUCED BRONCHIAL ASTHMA

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Abstract: The study basing on examination of 102 children with bronchial asthma defines indices of inflammatory activity in the airways and sets the diagnostic value of these indices as tests for verification exercise-induced bronchial asthma. The children with no signs of exercise-induced asthma compared to patients having them, were shown to experience some changes in the exhaled breath condensate, indicating a higher activity of inflammation in the airways. The content of nitrogen monoxide metabolites less than 50 mcmol/L or markers of proteolytic activity by azocol lysis less than 0.2 ml/hour in pulmonary expiration products increase the chances of having exercise-induced bronchial asthma phenotype with these tests sensitivity within 66.7-75.7%.

KeyWords: exercise-induced bronchial asthma, children, diagnostics, inflammation of airways, pulmonary expiration.

INTRODUCTION

According to the definition of PRACTALL [1], exercise-induced bronchial asthma (EIBA) is regarded as a type of asthma associated with exercise-induced transient bronchial obstruction [2, 3]. At the same time exercise-induced bronchospasm (EIBS) is objectively defined as reduction of FEV1 by 10% and more compared to the initial value after a bronchoprovocation test [4, 5]. The detection rate of EIBA and EIBS in pediatric populations varies in quite a wide range depending on the terminology, which the researchers prefer, choosing populations, using different objective criteria of the disease with an arbitrary choice of the distribution point of the results, taking into account factors that affect the severity of EIBA. The causal role of inflammation in exercise-induced bronchial obstruction in patients with bronchial asthma (BA) and people without the disease has been confirmed by many studies [6].

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For instance, based on the examination of patients with asthma and otherwise healthy children, we noted that in EIBA the rate of leukotrienes in exhaled breath condensate increased by half and reliably correlated with decreased FEV1 after exercise. It enabled to assume that leukotrienes, along with nitrogen monoxide, are actively involved in the development of exercise-induced bronchoconstriction [7]. Howerer, it should be noted that the role of nitrogen monoxide in the formation of EIBA is ambiguous. For instance, it was noted that its content in the exhaled breath condensate does not correlate with spirographic changes [8], but, in the event of EIBA, its content in exhaled air may increase, decrease or not change significantly [9, 10]. Still, the low level of NO in exhaled air can probably be seen as a marker of the absence of EIBA in screening studies in cohorts of young children suffering from asthma [11]. Thus, the available information concerning airway inflammation markers found in exhaled breath condensate, can now be considered contradictory and unclear.

2.1 Purpose

The aim of the study is to identify the signs of inflammatory activity in the airways of children with exercise-induced asthma.

2.2 Subjects & Methods

For this purpose we examined 102 schoolchildren with asthma at Pulmonary and Allergy department of Chernivtsi Regional Pediatric Hospital. In the article we used the classification and management of asthma according to "Unified clinical protocols of primary, secondary (specialized) medical care" Asthma in Children "(MOH of Ukraine number 868 of October 8, 2013) with the guidelines of The International global initiative for the diagnosis and treatment of asthma (GINA 2006-2010) [12-14], NAEPP-2008 [15], ICON-2012 [16], approvals PRACTALL-2008 [17] and national protocols of Australia (2008) [18], UK (2011) [19], Japan (2010) [20]. The diagnosis of exercise-induced asthma (EIBA) was formulated according to the recommendations of PRACTALL-2008 [17], the European Respiratory Society (ERS) and the European Academy of Allergology and Clinical Immunology (EAACI) in cooperation with GALEN (2008) [21].

The survey was conducted in parallel groups formed on the basis of a simple random selection using the "experiment-control" method. Based on the examination of the children, we formed two clinical groups. The first (Group I, basic) group included 50 schoolchildren diagnosed with EIBA, and the comparison group (Group II) consisted of 52 patients suffering from BA without signs of exercise-induced bronchospasm (EIBS). The average age of children in the first clinical group was 11.2±0.4 (95% CI 10.3-12.1) year. The first group involved 22 girls (44.0%) and 28 (56.0%) boys. Furthermore, 27 children (54.0%) were rural inhabitants and 23 patients (46.0%) were city dwellers. The average disease duration was 6.18±0.45 (95% CI 5.3-7.1) years. The second clinical group comprised 16 girls (30.8%) and 36 (69.3%) boys. The average age of patients in the second clinical group was 12.02±0.46 (95% CI 11.1-12.9) years and 25 children (48.1%) lived in the rural area while 27 patients (51.9%) were city dwellers. The average duration of disease reached 6.77±0.55 (95% CI 5.7-7.9) years. These data give reason to believe that comparison groups did not differ significantly in the main clinical characteristics, and therefore were comparable.

We identified inflammation signs in the exhaled breath condensate (EBC) of all the children: total protein by the method of Lowry O.H.[22]; concentration of nitrogen monoxide metabolites by N.L. Yemchenko [23]; markers of proteolytic activity by azoalbumin, azocasein and azocollagen lysis by K.N. Veremeyenko et al. [24]; the content of aldehid- and keto- secondary products of 2,4-dinitrophenylhydrazines (AKDNFH) of basic and neutral nature by O.E. Dubinina et al. [25]; catalase activity by M.A. Koroliuk et al. [26].

To determine the diagnostic value of the findings obtained in the comprehensive survey of children as the verification tests of EIBA, we determined their sensitivity as a test, specificity, predictive value of positive and negative results by defining confidence intervals (95% CI). Based on these characteristics of the test, we determined the ratio of reliability of positive and negative results, as well as post-test probability of the event with positive and negative test results. Risk assessment of the implementation of events was carried out on the basis of probability of relative, attributive risks and odds ratios events while defining their confidence intervals (95% CI).

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

It should be noted that the content of nitrogen monoxide metabolites (NMM) in exhaled breath condensate, which can be seen as an integral indicator of inflammatory activity, was reduced in children of the first clinical group compared to the comparison group of patients. For instance, the average content of NMM metabolites in patients with EIBA was 47.27±3.1 (95% CI 49.96-37.54) mmol/L. The representatives of the second clinical group

had the content of NMM metabolites in EBC as high as 48.78±3.67 (95% CI 56.27-41.29) mmol/L (P>0.05). Despite the absence of reliable inter-group differences, the frequency of found NMM metabolites in EBC content more than 50,0 mmol/L in the first group was 24.3% of cases and 39.4% of cases in the comparison group (P>0.05). Perhaps the lack of probable differences on this inflammatory marker is due to the fact that it reflects both the activity of the inflammatory process and its protective role in relation to the inflammation process.

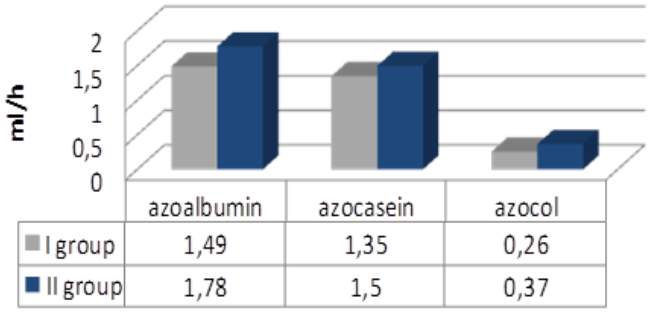
According to the literature, inflammation markers in the bronchi, which are found in EBC were supposed to be more pronounced in children of the second clinical group. Indeed, the content of products of protein peroxidation in EBC, which can be considered as an indicator of activity of oxidative stress in the bronchi, in these children was slightly higher than in patients with EIBA (Table. 1). However, a slight increase of total protein in EBC is likely to be regarded as an indicator of more pronounced vascular permeability that accompanies inflammation and can be seen as a manifestation of "leakage" syndrome.

Table 1.

Indices of lipid peroxidation in EBC in children of the comparison clinical groups (M±m)

Clinical groups	Number of children	Total protein, g/l	AKDNFH of basic nature, o.u.g of protein	AKDNFH of neutral nature, o.u.g of protein
Group I	30	3,76±0,23	48,51±6,69	9,4±2,49
Group II	41	4,22±0,27	50,8±5,62	5,89±0,63
P		>0,05	>0,05	>0,05
Note: P – Student's test; AKDNFH – aldehid- and keto- secondary products of 2,4-dinitrophenylhydrazines				

Proteolytic activity of EBC, expressed in ml/h, which can be regarded as an additional criterion for assessing the activity of inflammation in the bronchi, did not differ significantly in the comparison groups and tended to prevail in the second clinical group (Fig. 1).



Note: in all cases P>0.05

Fig. 1. Results of expired breath condensate proteolytic activity (ml/h on azoalbumin, azocasein and azocol lysis in the children under study

Lower activity of catalase in EBC that serves as a key enzyme of antioxidant bronchial defense must have contributed to the development of more active inflammation in the airways of children from the second clinical group. For instance, in children with no signs of EIBA the catalase activity in EBC amounted to 46.93±5.6 (95% CI 34.0-79.8) mmol/min x mg of protein, and 58.19±3.1 (95% CI 33.1-83.3) mmol/min x mg of protein in children of the first clinical group. The activity of catalase less than 40.0 mmol/min x mg of protein in patients with EIBA was found in 61.9% of cases and in those from the comparison group in 73.7% of cases.

According to current ideas, chronic inflammation of the airways, which in patients with clinically significant EIBS has more pronounced transitory nature is a basis of asthma pathogenesis and its particular phenotype EIBA [27]. Therefore, it was appropriate to study the diagnostic value of some signs of bronchial inflammation in EBC, in particular, the level of nitrogen monoxide metabolites (NMM), total protein and products of oxidative modification (basic and neutral AKDNFH). The results of this analysis are presented in Table 2. It should be noted that more sensitive tests (the content of nitrogen monoxide metabolites in EBC <50.0 mmol/L and total protein <4.0 g / L) increased the likelihood of post-test EIBA with positive result not more than by 5.0%.

Table 2.

Diagnostic value of some indices of the expired breath condensate for EIBA verification

Indices of EBC	Diagnostic value, % (95% CI)				Likelihood ratio	
	Sensitivity	Singularity	Prognostic value		Positive result	Negative result
			positive result	negative result		
Total protein < 4.0 g/l	63.3 (53-72)	48.8 (39-59)	55.3 (46-65)	57.1 (46-68)	1.24	0.75
Basic AKDNFH >55.0 o.u.g of protein	40.0 (30-50)	74.3 (65-83)	60.9 (48-73)	55.3 (46-64)	1.56	0.81
Neutral AKDNFH >10.0 o.u.g of protein	20.0 (13-29)	86.0 (78-92)	58.8 (41-75)	51.8 (44-60)	1.43	0.93
Nitrogen monoxide metabolites <50.0 mcmol/L	75.7 (66-84)	39.3 (30-50)	55.4 (47-64)	61.9 (49-74)	1.25	0.62
Azoalbumine lysis <1.2 ml/h	16.7 (10-25)	87.5 (79-93)	57.2 (38-75)	51.2 (43-59)	1.34	0.95
Azocasein lysis >1.5 ml/h	50.0 (40-60)	56.3 (44-66)	53.4 (43-64)	53.0 (43-63)	1.14	0.89
Azocol lysis <0.2 ml/h	66.7 (56-76)	50.0 (40-60)	57.2 (48-66)	60.0 (49-70)	1.33	0.67

At the same time, the content of basic and neutral AKDNFH in EBC increased the post-test likelihood of this phenotype in case of a positive result by 11.0% and 8.0%, respectively.

However, all of the suggested indices, meant, to some extent, a probable risk of realization of this phenotype of asthma in the examined patients (Table 3).

Table 3.

Clinical and epidemiological risk of EIBA depending on some indices of exhaled breath condensate

Indices of EBC	Odds ratio (95% CI)	Relative risk (95% CI)	Attributive risk
Total protein < 4.0 g/L	1.64 (0.9-2.9)	1.29 (1.0-1.6)	0.12
Basic AKDNFH >55.0 o.u.g of protein	1.93 (1.1-3.5)	1.36 (0.9-2.1)	0.16
Neutral AKDNFH >10.0 o.u.g of protein	1.54 (0.7-3.2)	1.22 (0.6-2.3)	0.11
Nitrogen monoxide metabolites <50.0 mcmol/L	2.02 (1.1-3.7)	1.45 (1.2-1.8)	0.17
Azoalbumin lysis <1.2 ml/h	1.4 (0.6-3.1)	1.17 (0.6-2.3)	0.08
Azocasein lysis >1.5 ml/h	1.29 (0.7-2.2)	1.13 (0.8-1.5)	0.06
Azocol lysis <0.2 ml/h	2.0 (1.13-3.6)	1.43 (1.1-1.8)	0.17

These findings give reason to believe that the probable risk of EIBA is indicated by higher sensitivity tests. However, it should be noted that, from a clinical point of view, the above mentioned risks of EIBA should be seen as rather modest arguments in favor of this phenotype of the disease.

4 CONCLUSIONS

Thus, the children with no signs of exercise-induced asthma compared to patients having them, experience some changes in the exhaled breath condensate, indicating a higher activity of inflammation in the airways. The content of nitrogen monoxide metabolites <50 mcmol/L or markers of proteolytic activity by azocol lysis <0.2 ml/h in pulmonary expiration products increase the chances of having EIBA phenotype with these tests sensitivity within 66.7-75.7%.

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PEDIATRICS

Gonchar M.O., Omelchenko O.V., Strelkova M.I., Yermolayev M.M.

DETECTION OF PSYCHOLOGICAL CHARACTERISTICS IN CHILDREN WITH CHRONIC GASTROINTESTINAL DISEASES USING MOS-SF-36 QUESTIONNAIRE

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Abstract: the article describes the main approaches in the study of psychological characteristics in children with chronic gastroenterological diseases according to MOS SF-36 questionnaire.

KeyWords: children, MOS-SF-36questionnaire, chronic gastrointestinal diseases.

INTRODUCTION

The World Health Organization defines Quality of Life as the individuals' perception of their position in life within the framework of culture and value systems they live in and in relation to their goals, expectations, standards and concerns [1].

Any disease affects both physical and psychological conditions, changing emotional reactions, place and role in everyday life. It is very important to get a complete picture of the disease impact on the most important functions when studying the nature of the disease. Identification of the exact type of abnormality and the level of severity is essential for the correct planning, treatment and rehabilitation. Physicians often assess only physical, laboratory and instrumental data describing only the physical condition of the patient. The majority of doctors are not interested in the information on individual psychological and social problems that have emerged due to the disease [2, 3].

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Evaluation of quality of life (QOL) has recently become an important new methodological approach to assess the results of medical interventions in clinical and epidemiological studies in the countries with high levels of health care because the traditional criteria of medical measures effectiveness, reflecting changes in the physical condition, do not give the full picture not only of the physical but also psychological and social condition of the patient. QOL research methodology enhances capabilities of standardization of treatment, provides individual monitoring with the evaluation of early and long-term results of treatment, develop predictive models of disease course and outcome in the practice of health care [4, 5]. In other words, it is a new integral approach to complex evaluation of the patient's health, that is based on the set of objective medical data and subjective evaluation of the patient.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

As the quality of life depends on the health status of children with chronic gastroenterological diseases, the purpose of the study was to assess physical and psychological presentation in children with gastroenterological disorders according to MOS SF-36 questionnaire.

2.2 Subjects & Methods

Quality of life was assessed in 66 patients aged from 2 to 17 years (of them, 32 girls (48.5%) and 34 boys (51.5%) with diseases of the digestive system. The average age of the patients was 11.3± 4.1 years. The survey respondents were treated at Gastroenterology department of Kharkiv Regional Children's Clinical Hospital within the period from 2015 to 2016.The control group consisted of 47 age- and gender matched healthy children (students of Merefa gymnasium No. 1). The average age was 12.1 ± 3.2 years; boys - 25 (48.1%) and girls - 22 (51.9%).

The examined children with gastrointestinal diseases were diagnosed with chronic gastritis (42.4%), biliary dyskinesis (15.2%), pancreatopathy (12.1%), duodenal ulcer (9.1%).

The quality of life was assessed with the help of the questionnaire. Patients or their parents completed questionnaires, and then its individual parts were analyzed with special scales or summary index.

The Short Form Health Survey (MOS SF-36) is one of the most common methods for evaluating the quality of life related to health. The questionnaire Medical Outcome Study- SF-36 consists of 36 questions forming the eight scaled scores, which are the weighted sums of the questions in their section: vitality (VT), physical functioning (PF), bodily pain (BP), general health perceptions (GH), physical role functioning (PR), emotional role functioning (RE), social role functioning (SF), mental health (MH).

The questionnaire assesses two components of health: physical and psychological. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The higher the score the less the disability, i.e. zero score is equivalent to maximum disability and a score of 100 is equivalent to absence of disability.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The survey patients with gastrointestinal abnormalities and children without digestive disorders gave answers, describing the quality of life. The survey results are presented inTable 1.

Table 1.

Quality of life in children with gastrointestinal diseases

	PF	RP	BP	GH	VT	SF	RE	MH
The main group N=66	76.7 ±6.4	71.2 ±4.9	69.1 ±5.3	56.3 ±6.4	64.4 ±4.4	68.9 ±6.4	70.7 ±3.3	64.7 ±7.6
The control group N=47	93.6 ±5.6	97.4 ±7.1	87.2 ±8.6	70.4 ±8.8	66.3 ±2.8	83.4 ±2.1	88.7 ±2.2	78.3 ±9.5

P < 0.05 for all parameters

Exacerbation of chronic gastrointestinal diseases causes pain, which is reflected in the reduction of bodily pain indices from 87.2 ± 8.6 to 69.1 ± 5.3. It is worth mentioning a decrease in the indices of physical activity from 93.6 ± 5.6 to 76.7 ± 6.4, significantly worsening emotional role functioning from 88.7 ± 2.2 to 70.7 ± 3.3. The ability to perform social responsibilities also reduced from 83.4 ± 2.1 to 68.9 ± 6.4. There was a decrease from 70.4 ± 8.8 to 56.3 ± 6.4 on general health scale. Physical condition also significantly declined from 97.4 ± 7.1 to 71.2 ± 4.9.

The received data provide evidence that the duodenum synthesizes regulatory peptides to support not only the digestive tract but also participates in neuroregulation (that is why it was called the "pituitary gland" of the gastrointestinal tract); also the results showed systematic changes of the microorganisms in local gastroduodenal lesions. Thus, there is a tendency to deterioration in each indicator of life quality, both on physical and psychological health scales.

4 CONCLUSIONS

The quality of life in children with gastroduodenal pathology is lower than in healthy children; it is mostly associat-

ed with a decrease in physical component. The most significant violations of life quality were observed in patients in role-functioning due to the physical component (RP) that lowered the ability to perform their daily social activities. The study also showed a reduction in such indices as bodily pain (BP) due to exacerbation of diseases of the digestive system; general health (GH) reduction was triggered by gastroduodenal abnormalities affecting the general condition of the patient and potentiating other organs and systems diseases. The psychological component of health was also affected mainly due to the emotional role functioning (RE). Thus, the quality of life in children with gastroenterological diseases reduced both by physical and psychological component.

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THEORETICAL AND EXPERIMENTAL MEDICINE

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RISK ASSESSMENT OF CHEMICALS IN FOOD AND IN SILICO TOXICOLOGY (SHORT OVERVIEW)

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Abstract: In the article current internationally accepted approaches to risk assessment of chemicals in food are described and relevant in silico (computational) methods that may be employed at different steps of risk assessment process for different types of chemicals in food are considered.

KeyWords: In silico Toxicology, Food safety, QSAR, Risk Assessment

INTRODUCTION

Food is composed of thousands of chemicals naturally occurring in particular food item as well as added by man along food chain or introduced unintentionally due to contamination from environment. Intentionally added chemicals are regulated with legal requirements for most of them regarding their toxicological assessment before adding into the food chain. Other ones, unintentionally introduced to food from the environment, naturally occurring or man-made, raise concerns for public health and are also extensively studied. Finally, the most numerous group of food chemicals are those which toxicological/biological properties are not fully understood or not understood at all. This article deals with consideration of internationally accepted approaches to risk assessment of chemicals in food and the role of the so-called “in silico” methods and future perspectives for their use.

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2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of this study was to describe current internationally accepted approaches to risk assessment of chemicals in food and determine relevant in silico methods that may be employed at different steps of risk assessment process for different types of chemicals in food.

Object of the study is in silico methodology and its application in risk assessment process of chemicals in food

2.2 Subjects & Methods

The study involved a review of regulatory governing acts with risk assessment of food safety issues and recent scientific literature on application of in silico methods for chemical hazard identification and characterization.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Risk assessment of chemicals in food. Definition, requirements, main steps and international guidelines

On the one hand, modern society substantially benefits from chemicals in everyday life, but on the other hand it faces a challenge of not introducing dangerous ones into

the environment or diet. For example, nearly 100,000 commercial chemicals have been inventoried in the USA, including 8,600 food additives, 3,400 cosmetic ingredients, 1,800 pharmaceuticals, and 1,000 active pesticide ingredients. [1]. Each year, estimated 2,000 new ones are introduced for use in such everyday items as foods, personal care products, prescription drugs, household cleaners, and lawn care products. We do not know the effects of many of these chemicals on our health, yet we may be exposed to them while manufacturing, distributing, using, and disposing them or when they become pollutants in our air, water, or soil. [2] To date, FAO-WHO Joint Expert Committee on Food Additives has evaluated more than 2600 food additives, approximately 50 contaminants and naturally occurring toxicants, and residues of approximately 75 veterinary drugs. [3]

Figure 1 presents a scheme classifying the types of food chemicals.

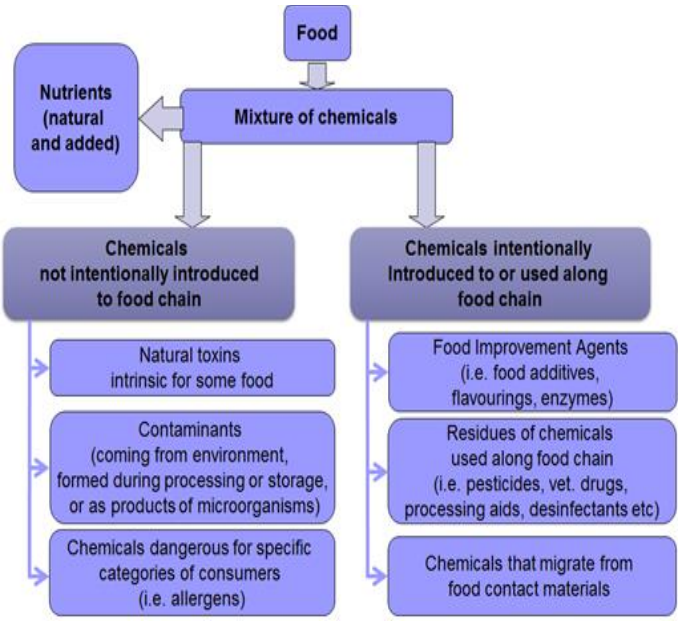

Figure 1. Food as a mixture of chemicals

Since food is a subject of international trade, its safety is regulated by multilateral agreements within World Trade Organization, namely WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). According to SPS Agreement, implementation of any requirements on food safety and "measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations" [4].

Being a member of WTO and in path to the European Union (EU), Ukraine has obligation to follow the rules of the SPS agreement. Accordingly, basic principles of the EU legislation on food safety include risk analysis as the cornerstone of food safety policy. [5] In Ukraine, Article 15 of the Law of Ukraine [6] provides that all food safety requirements should be based on scientific principles and current scientific justification and should be developed according to the results of risk assessment employing the methods of risk assessment elaborated by relevant international organizations. The Procedural Manual of the FAO/WHO Codex Alimentarius Commission provides internationally accepted definition of the relevant terms concerning risk analysis related to food safety [7].

It defines Risk Assessment as a scientifically based process comprising the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Figure 2 provides schematic representation of the whole process of risk analysis in food safety, as adapted from [8].

In silico methods used in risk assessment of food chemicals. Definition and types

According to the definition of the Royal Society of Chemists (2012), Predictive toxicology is concerned with the

Figure 2. Risk Analysis framework for food safety (adapted from [8])

development of new non-animal tests that do not simply duplicate existing animal tests but which provide a new scientific basis for safety testing.It reflects a paradigm shift from adverse effects observed in experimental animals, sometimes at high doses, to analyzing the effects of chronic exposures to low concentrations on cells and organ systems. It involves identification of significant perturbations of biological pathways at a molecular level to a cellular or organ level to predict outcomes [9].

Predictive toxicology is described as follows: “In predictive toxicology, we try to develop procedures (algorithms in computer science terms) that are capable to predict toxic effects (the output) from chemical and biological information (the input)” [10].

Tools of predictive toxicology include computational (in silico) modelling of biological activity (including toxicological endpoints), in vitro methods, OMICS technologies etc. The term “in silico” is used as an analogy to a generally used phrases in vivo and in vitro to describe any process performed on a computer or via computer simulation [11]. The United States Environmental Protection Agency (USEPA) defines in silico toxicology as the integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals. Broader understanding of in silico methodologies may be envisaged as anything we can do with a computer in toxicology. [12] Thus, the following types of in silico tools in toxicology may be distinguished:

1. Planning of experiments and power analysis
2. Data analysis procedures
3. Data mining and data-rich methods (e.g. data analysis procedures for omic and image analysis technologies)
4. Prediction models
5. Expert systems
6. (Quantitative) structure activity relationship (QSAR)
7. Modelling tools
8. Models of kinetics of substances (e.g. physiologically based toxicokinetic models)

Schematic representation of tools, steps to generate prediction models, and categories of prediction models adapted from [13] is given in Figure 3.

Speaking about hazard identification and characterization steps of risk assessment, Table 1 illustrates some of the currently available software and range of endpoints relevant to dietary risk assessment, as presented in [14].

European Food Safety Authority (EFSA - risk assessment agency in the field of food safety for EU) has thoroughly assessed applicability of in silico methods (namely QSAR, read across combined with threshold of toxicological concern (TTC) approach) for Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment [15].

For this purpose genotoxicity and carcinogenicity of such metabolites is a very important endpoint. Thus, application of integrated computational approaches including combined (Q)SAR models and read-across should be explored in future studies for the evaluation of genotoxicity alerts [16].

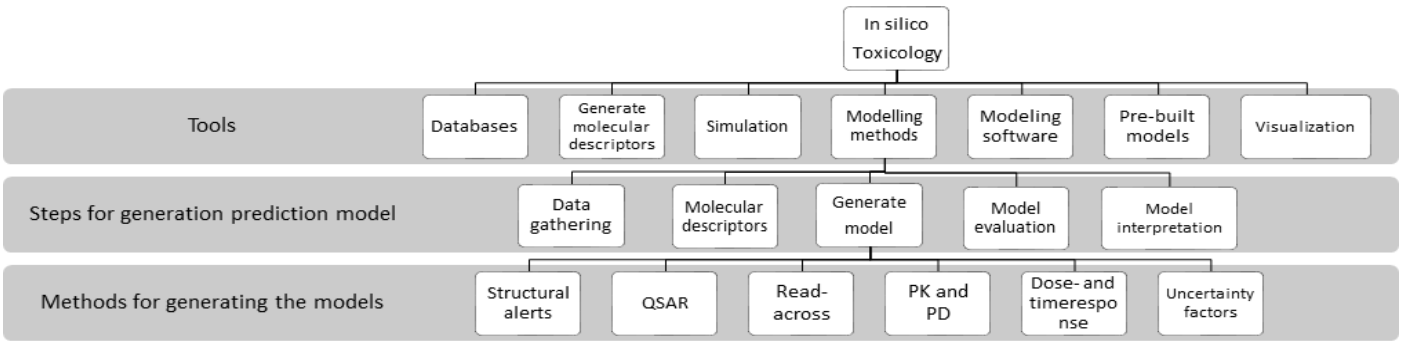

Figure 3. In silico toxicology tools, steps to generate prediction models, and categories of prediction models [13]

Table 1.

Software capable of predicting toxicological endpoints relevant to dietary risk assessment [14]

SOFTWARE	Acute oral toxicity	Repeat dose (chronic) oral toxicity	Genotoxicity (including mutagenicity)	Carcinogenicity	Reproductive (including developmental) toxicity	Endocrine activity / disruptiopn	Hepatotoxicity	Nephrotoxicity (+ urinary tract toxicity)	Neurotoxicity	Cytotoxicity	Immunotoxicity
ACD/Tox Suite (ToxBoxes)	*		*			*					
ADMET Predictor (Simulations Plus Inc.)		*	*	*		*	*				
BioEpisteme				*			*	*			
Caesar project models (Mario Negri Institute)			*	*	*						
Derek (Lhasa Ltd)			*	*	*	*	*	*	*		*
HazardExpert (CompuDrug)			*	*							
Lazar (In Silico Toxicology; Freiburg university)			*	*			*				
Leadscope (Leadscope)			*	*			*	*	*		
MCASE/MC4PC (MultiCASE)	*			*			*	*		*	
MDL QSAR (MDL)	*			*			*	*			
OASIS-TIMES (Laboratory of Mathematical Chemistry, Bourgas University)			*			*					
OncoLogic (US EPA)				*							
Pallas Suite including ToxAlert, Cytotoxicity (CompuDrug)			*	*					*	*	
TerraQSAR (TerraBase)	*					*					
TOPKAT (Accelrys)	*	*	*	*	*						
Toxtree (JRC)		*	*	*							
Molcode Toolbox (Molcode Ltd)		*	*	*		*				*	

US Food and Drug Administration (FDA) currently uses QSAR as a decision support tool in the safety evaluations of food-contact substances. This is a premarket evaluation in which the QSAR predictions are used in conjunction with literature search results and submitted toxicity tests. Occasionally, an impurity in a FCS with low dietary exposure may have only one genetic toxicity test submitted. In this case, QSAR results along with the genetic toxicity test and SAR analyses can be used to make a safety determination on the compound or provide sufficient support for recommending additional toxicity testing. [17]

Exposure assessment step of risk assessment also employs a number of in silico tools. One of them is MCRA (Monte Carlo Risk Assessment), which is a web-based system for probabilistic exposure and risk assessment of chemicals in the diet. Examples of this model and software validation for acute and chronic exposure assessment of pesticide residues in food are given in [18; 19]

Given that chemicals in food are regulated by different legislative acts, it is worth to mention that any method used for regulatory purposes should be validated and accepted. Rules for validation of QSAR methods are developed by Organization of Economic Cooperation and Development (OECD). The agreed OECD principles are as follows:

"To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1. a defined endpoint;
2. an unambiguous algorithm;
3. a defined domain of applicability;
4. appropriate measures of goodness-of-fit, robustness and predictivity;
5. a mechanistic interpretation, if possible" [20].

Furthermore, for a QSAR prediction to be adequate, it should be not only reliable (i.e. derived from a valid (Q)SAR model and within its applicability domain), but also relevant for regulatory decision. [21]

Figure 4 provides graphical representation of the criteria for identifying an adequate (Q)SAR model.

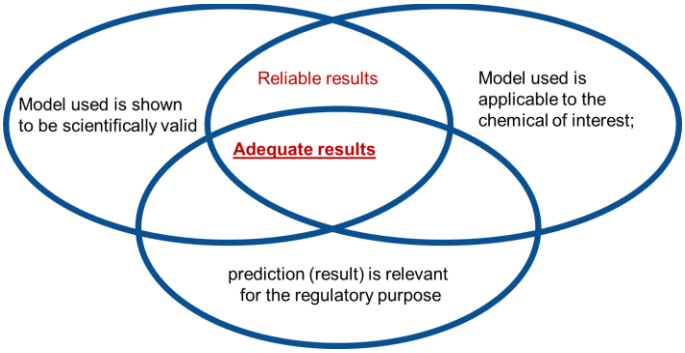

Figure 4 The overlapping considerations of validity, applicability and relevance needed to demonstrate (Q)SAR adequacy

4 CONCLUSIONS

Scientifically based risk assessment is required by legislation when new chemical food safety parameters are introduced. Huge number of chemicals to be assessed needs prioritization. Furthermore, toxicological testing of chemicals needs to be data driven. Both this tasks could be achieved and/or assisted by appropriately validated and adequate in silico tools. In fact, at each step of risk assessment process one or another computational tool has its role to play.

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THEORETICAL AND EXPERIMENTAL MEDICINE

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STATUS OF EUCHROMATIN IN NUCLEI OF PYLORIC MUCOUS CELLS AFTER INHALATION OF EPICHLO-ROHYDRIN AND CORRECTION OF EMERGING CHANGES

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Abstract: The study which involved examination by electronic microscopy determined that the area of euchromatin in one nuclei of gastric pyloric mucous cells of Albino outbred sexually mature adult male rats after inhalation of epichlorohydrin diminished as compared to the same index in rats of control group on 13.3% ($p<0.05$) and 7.4% ($p<0.05$) on the 1st and 30th day of supervision, respectively. Administration of both Echinacea purpurea extract and Thiotriazoline did not result in a change of euchromatin area. Employment of Echinacea purpurea extract in rats exposed to epichlorohydrin did not exert an impact on the duration and severity of the induced euchromatin area reduction. Application of Thiotriazoline secondary to epichlorohydrin exposure decreased the duration of the induced euchromatin area reduction.

KeyWords: pyloric glands, mucous cells, euchromatin in one nucleus, epichlorohydrin, Echinacea purpurea extract, thiotriazoline.

INTRODUCTION

The current state of population health depends on the degree of environmental pollution [2, 3]. There is pressure on ecological systems, among other factors determined by chemical pollutants, which come as a result of human activity in these systems [7, 8, 11]. One of the pollutants is epichlorohydrin [10]. The effect of epichlorohydrin results in the development of impairments in the organs of the immune, reproductive, respiratory systems, skin, eyes [1, 4, 5, 6, 9]. However, in the literature there are no data on the nature of epichlorohydrin action on the mucous membrane of the stomach and its action on the euchromatin in the nuclei of pyloric mucous cells.

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2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The objective of the research was to study the status of euchromatin in nuclei of pyloric mucous cells in rats after inhalation of epichlorohydrin and to provide evidence of the possibility of using an extract of Echinacea purpurea and Thiotriazoline for correcting the changes.

2.2 Subjects & Methods

The trial involved Albino outbred sexually mature adult male rats. The rats were divided into six experimental groups, each including thirty rats. Group I rats constituted Control Group. Group II rats were administered epichlorohydrin in a dose of 10 MPC (10 mg / kg) by inhalation for two months, five days a week for five hours a day. Group III rats were given Echinacea purpurea extract in a dose of 200 mg per kg of body weight through gastric tube for two months, five days per week. Group IV rats were administered Thiotriazoline in a dose of 117.4 mg per kg of body weight as an injection of 2.5% solution intraperitoneally for two months, five days a week. Group V rats were

exposed to epichlorohydrin and extract of Echinacea purpurea, and Group VI rats were exposed to epichlorohydrin and thiotriazoline according to the above described procedure. After two-month administration of epichlorohydrin, the extract of Echinacea purpurea and Thiotriazoline, six rats from each experimental group were taken out of the experiment on the first, seventh, fifteenth, thirtieth and sixtieth day. Examination with electronic microscope implied assessment of gastric fragments, which were placed in glutaraldehyde for 24 hours, and then to 1% osmium hydroxide for 1 hour. After dehydration the samples in increasing concentrations of ethanol and in absolute acetone material were filled with a mixture of epoxy resin (Epon-Araldite). The polymerization was carried out for 36 hours at a temperature of 60° C. Ultrathin slices were made on ultramicrotome UMTP-4 ("Electron" Sumy, Ukraine). The slices were contrasted in uranyl acetate solution and lead citrate according to Reynolds. Microscopy was performed using an electronic microscope EM-125 of the same manufacturer. The square of euchromatin in the nuclei of pyloric mucous cells was determined using "Microvisible" software company Micros (Austria). Excel software was used for statistical analysis of the results. Significance of differences was assessed using Mann-Whitney U test. The difference was considered significant at $p<0.05$.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Epichlorohydrin introduction decreased the square of euchromatin in one nucleus of mucous cell in the pyloric glands in comparison with the corresponding index in the rats of Control Group by 13.3% ($p<0.05$) on the first day, by 7.4% ($p<0.05$) on the thirtieth day after the inhalation cessation. It should be noted that the square of euchromatin in one nucleus of mucous cells in the pyloric glands in the rats undergoing the inhalation of epichlorohydrin increased by 13.1% ($p<0.01$) for the period from the first to the sixtieth day of observation (Table 1).

Table 1.

The square of euchromatin in one nucleus of pyloric mucous cell (M±MSD, μm)

Day of observation	Number of rats per group	Gp1	Gp2	Gp3	Gp4	Gp5	Gp6
1	n = 6	8.83 ±0.60	7.66* ±0.66	8.91 ±0.68	9.06 ±0.71	8.01* ±0.55	8.22* ±0.54
30	n = 6	8.82 ±0.55	8.17* ±0.63	8.80 ±0.61	8.98 ±0.66	8.27* ±0.44	8.68 ±0.57
60	n = 6	9.05 ±0.40	8.66 x ±0.42	9.37 ±0.54	9.17 ±0.69	8.72 x ±0.53	8.98 x ±0.52

Note:
1) * - $p<0.05$ in comparison with the indices in Control Group rats;
2) # - $p<0.05$ in comparison with the indices in rats that underwent epichlorohydrin inhalation;
3) x - $p<0.05$ in comparison with the indices in the rats of the same experimental group at different periods of observation.

Introduction of both the extract of Echinacea purpurea and Thiotriazoline did not lead to a change in square of euchromatin in comparison with the corresponding index in the rats of Control Group ($p>0.05$). The square of euchromatin in one nucleus of mucous cell in the pyloric glands in the rats of Group III and in the rats of Group IV did not change for the period from the first to the sixtieth day of observation ($p>0.05$).

Introduction of Epichlorohydrin and the extract of Echinacea purpurea decreased the square of euchromatin in one nucleus of pyloric mucous cell in comparison with the corresponding index in Control Group rats by 9.3% ($p<0.05$) on the first day, by 6.2% ($p<0.05$) on the thirtieth day after the introduction cessation. Statistically significant differences between the values of the square of euchromatin in Group II rats and Group V rats were absent at all stages of the research ($p>0.05$). The square of euchromatin in one nucleus of mucous cell in Group V rats became more by 8.9% ($p<0.05$) for the period from the first to the sixtieth day of observation ($p<0.05$).

The square of euchromatin in one nucleus of pyloric mucous cell decreased after introduction of Epichlorohydrin and Thiotriazoline in comparison with the corresponding index in Control Group rats by 6.9% ($p<0.05$) on the first day of observation. There were no differences between the values of the square of euchromatin in Group II rats and Group VI rats ($p>0.05$). The square of euchromatin in Group VI rats increased by 9.2% ($p<0.05$) during the time from the first to the sixtieth day of the research.

4 CONCLUSIONS

The experimental results indicate the presence of changes in the square of euchromatin in one nucleus of pyloric mucous cell in rats following inhalation of epichlorohydrin, allowing to draw the following conclusions:

1. Prolonged inhalation of epichlorohydrin is accompanied by a decrease in the square of euchromatin in one nucleus of pyloric mucous cell in rats, which remains after the completion of epichlorohydrin administration.

2. The introduction of both the extract of Echinacea purpurea and Thiotriazoline did not lead to a change in the square of euchromatin.

3. Administration of Echinacea purpurea extract in rats treated with epichlorohydrin had no effect on the duration and severity of the induced reduction of euchromatin square.

4. Administration of Thiotriazoline secondary to epichlorohydrin decreased the duration of euchromatin square reduction. Thiotriazoline softens the effect of reducing the square of euchromatin in the nuclei of mucous cells in the pyloric glands.

Prospects for further research. Continued investigation of the character of epichlorohydrin influence on the stomach will make it possible to find out the mechanisms of changes in the body in response to xenobiotics creating an experimental basis for the elaboration of promising ways to prevent the development of changes and their correction.

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THEORETICAL AND EXPERIMENTAL MEDICINE

Vorontsova L.L., Kovalenko V.A., Dub M.I., Zhuravlova M.Ye.

EFFECT OF ENDOTOXIN AGGRESSION ON THE DEVELOPMENT OF IMMUNE HOMEOSTASIS DISORDERS IN INFERTILE MEN

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Abstract: The article deals with the study of endotoxin-antiendotoxin system state showing that endotoxin aggression occurs in infertile men and transforms acute character (in considerable decrease in ejaculate fertility) into chronic one (in absolute deficiency of fertile properties in ejaculate). Changes in the indices of the impaired immune system link indicate an increase in tension, that, apparently assumes alternative available agents (in particular, gram-negative bacteria), which further disrupts spermatogenesis. It is possible to assume that endotoxin aggression, chronic in particular, is an important link of pathogenesis of male infertility, though high LPS concentrations potentiate immune phagocytic link, presumably, as a compensator.

KeyWords: endotoxin, innate immune system, male infertility.

INTRODUCTION

Infertility in marriage is a considerably widespread disorder. It is not only a medico-biological problem, but rather a social and demographic one [1]. Male infertility has been established to be the cause of infertile marriages in approximately 50% cases [2].

Spermogram is the most important investigation for diagnosis of male infertility. However, the results of diagnosis for male infertility are not always reliable: the obtained data demonstrate that fertility may be retained even in case when spermogram demonstrates deviations from the norm, and in contrast, infertility may be observed in men with normospermia [3]. The causes of deterioration for fertile characteristics in ejaculate are not known yet; thus, male infertility still presents challenges in diagnosis [4].

Some authors consider that inflammatory infections in different parts of urogenital tract trigger infertility [5].

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Infections are known to develop under certain conditions when the main links of immune system are impotent, but their influence on the development of pathology is often underestimated [6, 7].Recently there has been an increase in studies estimating the pivot role of the immune system in the pathology of male urogenital organs, but the state of phagocytic link in the immune system depending on the type of fertility impairment is under-investigated, moreover the obtained data are quite contradictory [8, 9].

In fact, spermatogenesis is one of the most dynamic process in the body and thus, it is utterly susceptible to injuring agents of both endogenic and exogenic origin [10]. Endotoxin (ET) of gram-negative bacteria is one of the most important agents in forming endogenic intoxication syndrome, as it exerts exceptional biologic activity and is one of the most potent exogenic modulators for immune reactivity [11]. The main pathophysiologic effect of ET consists in induction of ejecting some endogenic mediators for inflammation that are mainly synthesized by myelomonocytic cells [12]. Neutrophils and macrophages activated by ET release considerable amount of free radicals resulting in further destabilization of biologic membranes and, consequently, in potential cytostatic effect for bacterial toxins [13].

Thus, the so-called "vicious circle" is formed, where

disrupted biocenosis promotes local immunity suppression determining conditions of pathogenic influence of commensals secondary to immunosuppression that potentiates immune impotence [14,15].

However, the mechanism of bacterial LPC or endotoxins effect on the immune system is rather complicated and is still under-investigated.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

Having regard to the above, the aim of our study is to assess the influence of endotoxin in gram-negative bacteria on the state of phagocytic link of the immune system in men with fertility impairment in ejaculate.

2.2 Subjects & Methods

The study involved 54 men aged from 20 to 45. They signed a written agreement to participate in investigations. This agreement was submitted to the approval of Bioethics committee at SE "Zaporizhzhya Medical Academy of Post- Graduate Education of the Ministry of Health of Ukraine" in accordance with ethic, moral and legal requirements by the order of the Ministry of Health of Ukraine No. 281of 01.11.2000.

All men were divided into three groups. The first group (control one) consisted of 20 healthy men without any impairments of the reproductive system; they had 1-2 children aged 1-2. The second group comprised 19 men with decreased fertility in ejaculate. The third group included 15 men whose ejaculate was found to lack fertile properties. The men of the second and third groups were in childless marriages from one to fifteen years.

Each patient was referred to microbiologic examination of ejaculate according to the Order of the Ministry of Health of USSR No. 535 of 22.04.1985 "Unification for microbiologic (bacteriologic) examinations used in clinical and diagnostic laboratories at medical institutions". Bacteriologic investigation of ejaculate in men of the second and third groups showed bacteriospermia caused by gram-positive and gram negative flora.

All the men were referred to a comprehensive examination including spermogram analysis according to the WHO recommendations [16] and assessment of the state of phagocytic link of immune and endotoxin-antiendotoxin systems.

The assessment on phagocytic activity of neutrophils and monocytes in blood was carried out by the technique based on identification of their absorbing and digestive capacity 30-120 minutes after preincubation with 24 hours culture of Staphylococcus epidermis strain [17]. Neutrophils oxygen-depending metabolism (NBT-test) and functional cell reserve (NBT-test stimulated) were assessed by the cell ability to restore nitro-blue tetrazolium after M.E.Wiksman and A.N. Mayansky [18].

The assessment for total concentration of endotoxin (ET) in systemic blood circulation was performed using "Micro-LAL-test". To assess humoral link of antiendotoxin immunity antibodies titers to glycolipid (At to GLP) and general enterobacterial antigen (At to GEA) were identified by "SOIS- IFA" technique. Statistical data processing was performed with STATISTICA (StatSoftStatistica v. 6. 0.) software using Wald-Volkovits test. The difference was considered reliable when the achieved value was <0.05. The data under investigation were presented as median (ME) and interquartile swing (RQ), presenting the difference between the values of 75-th and 25-th percentiles (RQ= 75% UQ= 25% LQ) where UQ is the upper quartile and LQ is the lower one.

Conflict of interests
There is no conflict of interests.

3 RESULTS AND DISCUSSION

Our microbiologic examination of ejaculate showed that microorganisms isolated from the samples of infertile men had both gram-positive and gram negative bacteria (E. Coli, Ent. faecalis, S., Str., as well as coagulo-negative and coagulo-positive and Candida fungi. Comparative test for microbiocenosis of ejaculate in infertile men showed that in 80% men of the second group (decreased ejaculate fertility) conventionally pathogenic flora was presented by Ent. faecalis, S. haemolyticus in concentrations from 10 to 10 UFC/ml, C. albicans – 10 UFC/ml and S.epidermis had poor growth. Whereas in the third group (ejaculate without fertile properties) pathogenic flora was presented by Str. Mitis – 10 UFC/ml, S. epidermis – 10 UFC/mg, S. haemolyticus - 10 UFC/ml, E.coli – 10 UFC/ml, Klebsiella pneumonia – 10 (4) UFC/ml.

Microbiologic findings did not provide any undisputable information concerning the influence of changes in microbiocenosis on ejaculate fertile properties. They only confirmed the presence of changes. Taking into account that bacterial associations revealed the ability to decrease unspecific reactivity that often leads to chronic inflammation, further dissemination of mixed infection and obviously, infertility, it is necessary to conduct extended studies regarding the influence of bacterial infection on male infertility and particularly, the impact of the endotoxin-antiendotoxin system state on male reproductive performance.

Assessment of endotoxin-antiendotoxin system in men of the second group showed a considerable increase in ET concentration in general blood circulation in 1079 % as compared to the control group (Table 1).

The study showed a tendency to increasing titers At to GLP and At to GEA in 11% and 8% as compared to control indices, respectively. Thus, an increase in ET occurred secondary to an increase in activity for humoral link of antiendotoxin immunity that proves acute EA in this group of men. Evaluation of endotoxin-antiendotoxin system in men of the third group revealed a considerable increase in ET concentration almost 25-fold (in 2389%) as compared to the control group.

Table 1.
The state of endotoxin-antiendotoxin system in men suffering from different types of ejaculate fertility impairment, Me (75%Q – 25%Q = RQ)

Index, unit of measure	ET concentration, UFC/ml	Antibodies titer to GLP, c.u.	Antibodies titer to GEA, c.u.
Group1 (n = 20)	0.19 (0.21 – 0.18 = 0.03)	195.2 (196.1 – 193.9 = 2.2)	389.4 (389.8 – 388.9 = 0.9)
Group 2 (n = 19)	2.24* (2.34 – 1.98 = 0.36)	216.0 (218.4 – 213.8 = 4.6)	421.1* (424.7 – 419.3 = 5.4)
Group 3 (n = 15)	4.73* (4.80 – 4.43 = 0.37)	116.9* (120.6 – 112.2 = 8.4)	291.2* (300.4 – 289.6 = 10.8)

Note: * statistically significant difference ($p < 0.05$) as compared to the control group.

The rate At to GLP and At to GEA was decreased in 40% and 25% as compared to the control group, respectively. Thus, a considerable increase in ET rate in blood circulation in men of the third group was observed secondary to a sharp decrease in the activity of humoral link of antiendotoxin immunity which indicates the development of chronic EA in this group.

Assessment of indices for functional and metabolic status of neutrophils and monocytes (Table 2) in men with decreased fertility in ejaculate (second group) as compared to the control values of a decrease in functional activity of neutrophils was revealed both at the 30th minute and at the 120th minute in 13% and 9%, respectively, but the latter case was statistically unreliable though clinically significant. Absorptive capacity of neutrophils at the 30th minute coincided with the control indices, but at the same time digestive capacity of neutrophils was increased in 27%, respectively to the values of the control group.

Functional activity of monocytes (NPI) at the 30th minute in the second group corresponded to the control group. Functional activity of monocytes at the 120th minute exceeded the control values in 22%. Absorbing and digestive capacity of monocytes was increased in 7% (statistically unreliable, but clinically significant) and they were increased in 18% as compared to the control values, respectively.

Table 2.

The state of metabolic and functional status of neutrophils and monocytes in men with different impairments of ejaculate fertility, Me (75%Q – 25%Q = RQ)

Index, unit of measure	1st group (n = 20)	2nd group (n = 19)	3rd group (n = 15)
NPI at 30 min., %	58 (74 – 29 = 45)	50.5 (59.0 – 41.0 = 18)	48* (52 – 38 = 14)
NPN at 30 min., c.u.	1.8 (6.5 – 1.3 = 5.2)	1.85 (3.0 – 1.4 = 1.6)	1.5*.** (1.8 – 1.3 = 0.5)
NPI at 120 min., %	50 (68 – 29 = 39)	45.5 (52.0 – 40.0 = 12)	54 (57 – 39 = 18)
NPN at 120 min, c.u.	1.3 (3.1 – 1.1 = 2.0)	1.7* (2.2- 1.2 = 1.0)	1.5** (1.8 – 1.3 = 0.5)
MPI at 30 min., %	28 (30 – 20 = 10)	29 (45 – 24 = 21)	30 (30 – 22 = 8)
MPN at 30 min., c.u.	1.4 (1.7 – 1.0 = 0.7)	1.5 (1.9 – 0.9 = 1.0)	1.7 (1.7 – 1.0 = 0.7)
MPI at 120 min, %	20 (25 – 16 = 9)	24.5 (54.0 – 20.0 = 34)	28* (35 – 24 = 11)
MPN at 120 min., c.u.	1.1 (1.5 – 0.8 = 0.7)	1.3 (3.1 – 0.7 = 2.4)	1.5* (1.7 – 1.0 = 0.7)
NBTsp., c.u..	1.2 (1.3 – 1.0 = 0.3)	1.5 (1.9 – 0.7 = 1.2)	1.1 (1.5 – 1.0 = 0.5)
NBTsp., c.u..	1.4 (1.5 – 1.0 = 0.5)	1.8* (2.2 – 0.7 = 1.5)	1.1 (1.4 – 0.9 = 0.5)

Note: * statistically significant difference (p< 0.05) as compared to the control group; ** statistically significant difference (p< 0.05) as compared to the 2nd group.

The study also involved evaluation of peculiarities of the development of phagocytizing cells with NBT-test as an index. Spontaneous NBT-test displays a degree in functional irritation of phagocytizing cells. Stimulated NBT-test characterizes potential activity of phagocytizing cells and is considered to be a biochemical criterion for their readiness to complete phagocytosis. It mainly concerns blockade for producing oxygen-depending bactericidal agents. The second group was shown to have increased activity of phagocytizing cells both in spontaneous NBT-test in 25% and in stimulated NBT-test in 29% as compared to healthy men.

Thus, in men with decreased fertility phagocytic number of neutrophils and monocytes both at absorbing and digestive stage indicated completed phagocytosis. Indices increased through NBT-test suggested tension in unspecific link of the immune system.

4 CONCLUSIONS

1. Evaluation of endotoxin-antiendotoxin system state showed that endotoxin aggression occurring in infertile men transforms acute character (in considerable decrease in ejaculate fertility) into chronic one (in absolute deficiency of fertile properties in ejaculate).

2. Changes in indices of the impaired immune system link indicate increased tension, which definitely assumes alternative available agents (in particular, gram-negative bacteria) with further impairment of spermatogenesis.

3. It is possible to assume that endotoxin aggression and chronic in particular, is an important link for pathogenesis of male infertility, though high LPS concentrations potentiate immune phagocytic link, presumably, as a compensator.

4. Assessment of endotoxin-antiendotoxin system in men with reproductive function impairment is an indispensable component of comprehensive examination aimed to improve diagnosis of male infertility and promote planning of therapeutic management based on pathogenesis.

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PATHOLOGY

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THORACO-OMPHALOPAGUS CONJOINED TWINS (case report)

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Abstract: Conjoined twins develop due to impairment in embryo division process. There are some risk factors considered to increase the incidence of this condition. However, it is necessary to perform further investigation of genetic processes as well as teratogenic agents involved. In this study we review a case of an 18-year old patient with the first pregnancy, having no apparent teratogenic factors or family history, diagnosed with conjoined twins. An abortion was performed on the 13th-14th weeks of gestation. Multiple malformations of conjoined twins were studied and genetic counseling was prescribed to the patient during planning of the next pregnancy.

KeyWords: conjoined twins, thoraco-omphalopagus twins, malformations.

INTRODUCTION

Conjoined twins are monozygotic twins, formed as a result of incomplete division of the embryo, having common extraembryonic organs: chorion, amnion, placenta. The incidence of this condition ranges from 1:50,000 to 1:200,000 births [1, 2]. Understanding exact mechanisms triggering the formation of conjoined twins requires further investigation. It is assumed that the late embryo division, which occurs on days 13-15 of the development, is the leading reason of non-separation of the twins. The conjoined twin formation is associated with the development of anomalies of the twins and a high perinatal mortality rate. Considering the above mentioned, the study assessed the role of ultrasound diagnosis in the management of conjoined twin pregnancies.

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CASE STUDY

An 18-year-old patient K. at 13th-14th week of gestation of the first pregnancy was referred for planned ultrasonography. Ultrasonography showed multiple fetal malformations. She was found to have conjoined twins, hypoplasia of both fetal nasal bones, cystic hygroma in the occipital region of one fetus. The bones of the pelvis and lower extremities of one fetus were not detected. An abortion for medical reasons was recommended and the patient was admitted to Odessa Regional Clinical Hospital. According to the collected data, the course of pregnancy was normal and there were no cases of hereditary diseases in the family history. An abortion was performed and the abortion material was sent to Odessa Regional Pathologic Bureau. The fetuses were labeled as fetus No.1 and fetus No.2 and referred to autopsy. The fetuses were joined in the chest and abdomen areas (Terata Anacatadidyma) (Fig. 1).

Fetus No.1. The brain (3.5 x 2.5 x 2 cm) was formed according to the stage of the development, lateral ventricles were slightly expanded and meninges were plethoric. The heart (1.2 x 0.7 x 0.7 cm) was visualized under the sternum following the dissection of the chest. The heart had a normal structure with only one vessel leaving it (aorta) and was not covered by pericardium. The esophagus and the

trachea were without abnormalities. The spleen and kidneys were located at normal anatomical sites.

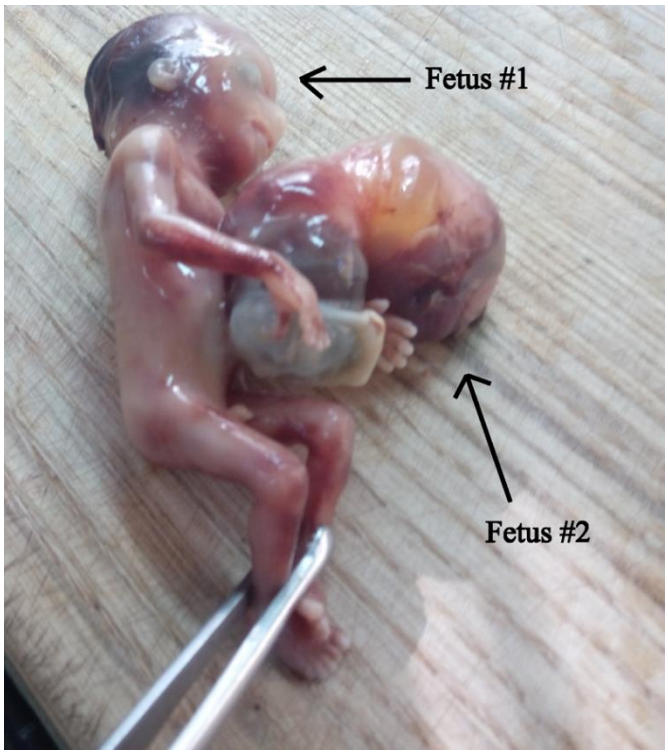

Figure 1. The fetuses joined in the chest and abdomen were labeled fetus No.1 and fetus No.2.

Fetuses had one common abdomen (Fig. 2). The abdominal cavity was found to have common intestines and common liver (spherical form, 2.5 x 2 x 1.5 cm) with a gallbladder.

Fetus No.2. There was severe edema and a closed cavity (4 x 2.5 x 1 cm) filled with transparent, slightly yellowish contents in the occipital area. The neck was drastically shortened. The fetus was found to have humerus bud. The brain (2.5 x 2.3 x 3.2 cm) was formed according to the stage of the development, meninges were plethoric. The heart (0.9 x 0.5 x 0.5 cm) had cervical ectopy and was not covered by pericardium and with only two chambers inside.

The examination determined lung aplasia.

The bones of the pelvis and lower extremities were not detected.

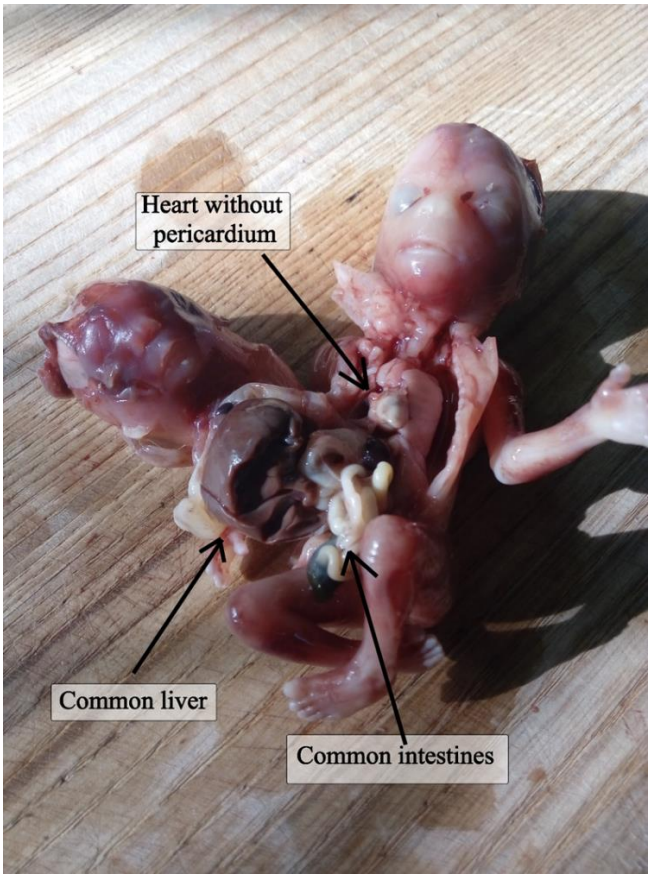

Figure 2. Common abdomen in fetuses. Common intestines and common liver with a gallbladder in the abdominal cavity.

The common liver was connected with the heart through the blood vessel (Fig. 3).

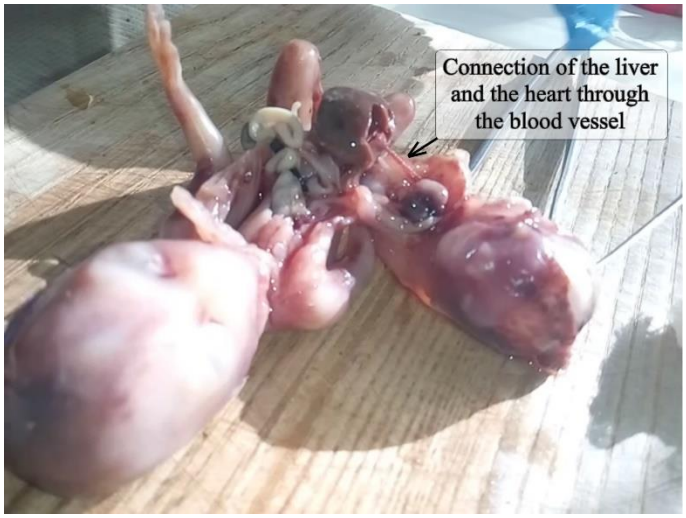

Figure 3. Common liver connected with the heart of fetus No.2 through the blood vessel.

The autopsy findings were confirmed by investigation of histological material.

DISCUSSION

After the fertilization, a zygote is going through a number of stages resulting in a formation of the fetus. Sometimes a zygote or an embryo divides, resulting in the formation of two fetuses. This process is very rare (6-9 cases per one thousand births during natural pregnancy [3]). Normally in monozygotic twins, an embryo division occurs from the 2nd to the 7th days of the development, leading to the formation of two separate fetuses. Sometimes, under uncertain mechanisms, this process can be prolonged up to 13-15 days and terminated with an incomplete division. In this case, both fetuses have common extraembryonic organs and are joined in different parts of their bodies, or even sharing common organs [4]. In some clinical cases it is possible to perform surgical separation, but it entails additional risks and can be life-threatening to one or both of the twins, especially when the surgery affects vital organs [5]. Sometimes, as in the present clinical case, surgery is impossible or it is of no use due to multiple malformations of the fetuses [6]. Etiology of the formation of conjoined twin is still uncertain, but some assumptions can be made: for example, there are authors indicating assisted reproductive technologies as a risk factor. Some studies showed that 14.8% of 75 pregnancies with conjoined twins were observed in pregnancies after artificial ferilization [7]. Such techniques as ovulation induction, intracytoplasmic sperm injection and assisted hatching may play a significant role in the failure of an early embryo division [8] but the amount of such investigations is considered not sufficient. In both natural pregnancy and assisted reproduction, some teratogenic agents (griseofulvin [9] or ionizing radiation, as in the case of Chornobyl-impacted regions [10]) and genetic impairments [1, 11] significantly increase the risk of the formation of conjoined twins, but no unified point of view has been suggested at this point. Unexplained etiology and mechanisms of formation of conjoined twins determine the necessity of thorough management of physiological pregnancy and increase the role of ultrasound diagnosis, which can detected formation of conjoined twins as early as at 7-9th weeks of gestation [12].

4 CONCLUSIONS

Couples with conjoined twins in family history should undergo genetic counseling to consider all possible risk factors.

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DENTISTRY

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MANDIBULAR OSTEOMETRIC INDICES IN PATIENTS WITH PERIODONTITIS DEPENDING ON VITAMIN D LEVEL

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Abstract: Recent studies have reported a relationship between vitamin D level, bone tissue and periodontitis. The aim of study was to determine mandibular osteometric indices in patients with periodontitis depending on the level of vitamin D. We have examined 95 patients with periodontitis. Patients were divided into 3 groups according to 25-hydroxyvitamin-D concentration in plasma. All patients were examined to determine vitamin D level and mandibular osteometric indices. Mandibular height in the canine area in patients with vitamin D sufficiency was the lowest and was 27.33(25.15-29.02)mm. Mandibular height in patients with vitamin D deficiency and insufficiency was 28.04(25.91-29.78)mm and 29.03(26.70-31.21)mm, respectively. Mandibular body height in the canine area in patients with GP and vitamin D deficiency, insufficiency and sufficiency was 16.68(14.95-18.45)mm, 17.34(15.74-19.42)mm and 15.93(14.65-17.23)mm, respectively and alveolar bone height in canine area was 11.55(9.53-12.85)mm, 11.21(10.00-13.81)mm and 11.21(9.69-12.75)mm, respectively. Thus, the increase of mandibular height in patients with periodontitis who had vitamin D deficiency and insufficiency occurred by the increase of mandibular body height.

KeyWords: periodontitis, vitamin D, bone tissue, mandible, osteometric indices.

INTRODUCTION

Vitamin D plays an important role in prevention of many diseases, including rickets, osteoporosis, both types of diabetes mellitus and others [1-4]. Its deficiency and insufficiency are widespread in Ukraine and worldwide [5-7]. Periodontitis is also widespread throughout the world. It is characterized by inflammation in the periodontal tissues, alveolar bone loss, resulting in the occurrence of tooth mobility and tooth loss. Some studies showed an increase in mandibular body in patients with periodontitis [8,9]. In particular, Mazur demonstrated that the height of mandible body increased in an experimental model in rats with periodontitis. This happened as a result of the alveolar bone loss. The incidence of vitamin D deficiency and periodontitis determines the relevance of studying their relationship. Many authors noted the existence of that relationship [10-13].

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In particular, Dietrich et al. showed a negative correlation between 25-hydroxyvitamin-D3 concentration and periodontal disease in men and women aged 50 years (the greater 25-hydroxyvitamin-D3 concentration, the lower the level of clinical attachment loss) [10]. Studying the relationship between 25-hydroxyvitamin-D (25(OH)D) concentration and periodontal disease in women during pregnancy Boggess et al. concluded that periodontal disease in pregnant women was associated with 25(OH)D levels below 75 nmol/L [12].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

The aim of study was to determine mandibular osteometric indices in patients with periodontitis depending on the level of vitamin D.

2.2 Subjects

The study involved 95 (60 women (63.2%) and 35 men (36.8%, mean age 43.21 ± 11.77 (M ± SD) years) patients with periodontitis who were examined within the period from March 2012 to January 2016. The

patients were divided into 3 groups according to plasma 25(OH)D concentration. Group 1 included 21 patients with vitamin D sufficiency. Group 2 consisted of 40 patients with vitamin D insufficiency. Group 3 included 34 patients with vitamin D deficiency. The distribution of patients into the groups depending on the level of vitamin D is presented in Table 1.

Table 1.

Patients distribution into groups depending on the level of vitamin D (vitamin D level, the number of patients and age of patients in groups)

Groups	Number of patients, n	Number of patients, %	Age Me (IQR)	Vitamin D level (ng/mL) Me (IQR)
Group 1 (vitamin sufficiency)	21	22.1	42.00 (31.50-53.00)	35.90 (32.43-40.45)
Group 2 (vitamin D insufficiency)	40	42.1	42.00 (33.75-50.75)	23.52 (21.33-26.17)
Group 3 (vitamin D deficiency)	34	35.8	42.00 (31.75-48.25)	15.08 (12.11-17.79)

2.3 Methods

Diagnosis of periodontitis was established according to the Danilevsky classification (1998). [14]. Clinical examination methods included the presence of gums bleeding, periodontal pockets and clinical attachment loss (periodontal probe using) determination. Other means included radiological methods of examination (panoramic radiographs) and osteometric methods.

To determine the relationship between 25(OH)D level and compensatory mechanisms in mandible the study implied determination of mandibular height, mandibular body height, alveolar bone height in canine area and mandibular cortical width [15]. Mandibular body height was defined as the length of the perpendicular lowered from the canine root apex to the bottom of the mandibular cortical plate. Mandibular body was measured on both sides of the mandible, and their average value was calculated statistically. The height of the mandible was determined in two parts of the mandible: in the canine area and in the mental foramen area. Mandibular height in the canine areas was defined as the length of the perpendicular lowered from the top of mandibular alveolar bone in canine areas to the bottom of the mandibular cortical plate. Mandibular height in canine area was measured on both sides of the mandible, and their average value was calculated statistically. Mandibular height in mental foramen area was defined as the length of the perpendicular lowered from the top of mandibular alveolar bone to the bottom of the mandibular cortical plate through the middle of mental foramen. Mandibular height in mental foramen area was measured on both sides of the mandible, and their average value was calculated statistically. Mandibular alveolar bone height in canine area was defined as the length of the perpendicular lowered from the top of mandibular alveolar bone to the canine root apex. Mandibular alveolar bone height was measured on both sides of the mandible, and their average value was calculated statistically. Mandibular cortical width was defined as the length of the perpendicular lowered from the top of mandibular cortical plate to the bottom of mandibular cortical plate below the mental foramen. Mandibular cortical width was measured on both sides of the mandible, and their average value was calculated statistically. The methods for measuring of mandibular height in canine area and in mental foramen area, mandibular body height, alveolar bone height in canine area and mandibular cortical width are presented in Figure 1.

To verify the diagnosis of vitamin D deficiency and insufficiency we used classification (2011) adopted by the International Institute of Medicine and Endocrine Society Clinical Practice Guideline. According to this classification vitamin D deficiency was observed when vitamin D level was less than 20 ng/mL, insufficiency when vitamin D level was from 20 to 30 ng/mL and sufficiency when vitamin D level was from 30 to 50 ng/mL [16].

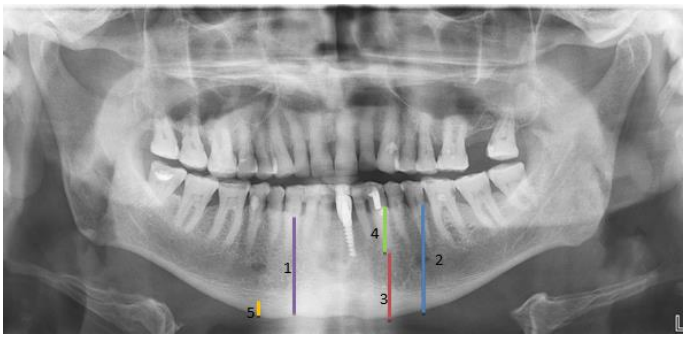

Figure 1. Methods for measuring of mandibular height in canine area and in mental foramen area, mandibular body height, alveolar bone height and mandibular cortical width (1 - mandible height in canine areas; 2 - mandibular height in mental foramen area; 3 - mandibular body height; 4 - alveolar bone height in canine area; 5 - mandibular cortical width)

Statistical analysis was performed using statistical software package (SPSS version 20).

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

To determine mandibular osteometric indices in patients with periodontitis depending on the level of vitamin D we measured mandibular height in canine area and in mental foramen area, mandibular body height and alveolar bone height in canine area. The results of the study demonstrated that the lowest mandibular height in the canine area was observed in patients with periodontitis and vitamin D sufficiency. Mandibular height in the canine area in patients with vitamin D insufficiency was significantly higher than in patients with vitamin D sufficiency (p = 0.054). In the study of mandibular body height the patients with vitamin D sufficiency were found to have the lowest mandibular body height in the canine area and it constituted 15.93 (14.65-17.23) mm. Mandibular body height in the canine area in patients with vitamin D insufficiency was significantly higher than in patients with vitamin D sufficiency (p = 0.049). There was no significant difference between alveolar bone height in canine area in patients with periodontitis depending on the level of vitamin D (p > 0.05). The values of osteometric indices (mandibular height in canine area and in mental foramen area, mandibular body height and alveolar bone height in canine area) in patients with periodontitis depending on the level of vitamin D and their statistical comparison are presented in Table 2.

Table 2.

Values of osteometric indices (mandibular height in canine area and in mental foramen area, mandibular body height and alveolar bone height in canine area) in patients with periodontitis depending on the level of vitamin D

Index	Vitamin D level			Comparison	
	Sufficiency	Insufficiency	Deficiency	Gp.	p
	Me (IQR)	Me (IQR)	Me (IQR)		
Mandibular height in canine area, mm	27.33 (25.15-29.02)	29.03 (26.70-31.21)	28.04 (25.91-29.78)	1-2	0.054
				1-3	0.319
				2-3	0.222
Mandibular body height, mm	15.93 (14.65-17.23)	17.34 (15.74-19.42)	16.68 (14.95-18.45)	1-2	0.049*
				1-3	0.350
				2-3	0.269
Alveolar bone height in canine area, mm	11.21 (9.69-12.75)	11.21 (10.00-13.81)	11.55 (9.53-12.85)	1-2	0.635
				1-3	0.609
				2-3	0.883

* Significant differences between the groups

The results of the study of mandibular height in mental foramen area demonstrated that the lowest mandibular height in mental foramen area was observed in patients with periodontitis that have vitamin D sufficiency and was 26.03(23,65-27,68) mm. In patients with vitamin D deficiency and insufficiency mandibular height in mental foramen area was 28.03(25.90-31.17) mm and 26.56(24.45-28.38) mm respectively. Mandibular height in mental foramen area in patients with vitamin D insufficiency was significantly higher than in patients with vitamin D sufficiency (p = 0.010). There was no significant difference between mandibular cortical width in patients with periodontitis depending on the level of vitamin D (p > 0.05). The values of mandibular height in mental foramen area and mandibular cortical width in patients with periodontitis depending on the level of vitamin D and their statistical comparison are presented in Table 3.

Therefore the results of the study showed that mandibular height in mental foramen area and in canine area were the lowest in patients with periodontitis that have vitamin D sufficiency.

Table 3.

Values of osteometric indices (mandibular height in canine area and in mental foramen area, mandibular body height and alveolar bone height in canine area) in patients with periodontitis depending on the level of vitamin D

Index	Vitamin D level			Comparison	
	Sufficiency	Insufficiency	Deficiency	Gp.	p
	Me (IQR)	Me (IQR)	Me (IQR)		
Mandibular height in mental foramen area, mm	26.03 (23.65-27.68)	28.03 (25.90-31.17)	26.56 (24.45-28.38)	1-2	0.010*
				1-3	0.188
				2-3	0.175
Mandibular cortical width, mm	3.64 (3.16-4.16)	3.44 (2.87-4.18)	3.83 (3.07-4.30)	1-2	0.403
				1-3	0.749
				2-3	0.270

* Significant differences between the groups

Increasing of mandibular height in patients with periodontitis that had vitamin D deficiency and insufficiency was due to a compensatory increase of mandibular body height. This increase might occur as a compensatory mechanism of the mandible to chewing that load by the loss of alveolar bone of mandible. This can be due to the increase of bone metabolic activity that occurs on the background of vitamin D deficiency and insufficiency [17].

4 CONCLUSIONS

1. The relationship between vitamin D level and mandibular osteometric indices in patients with periodontitis exists.

2. The lowest mandibular height in mental foramen area and in canine area was observed in patients with periodontitis that occurs on the background of vitamin D sufficiency.

3. The increase of mandibular height in patients with periodontitis who had vitamin D deficiency and insufficiency occurred by the increase of mandibular body height.

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DENTISTRY

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THE INCIDENCE OF ORAL MALIGNANCIES IN POLTAVA REGION IN 2011-2015

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Abstract: 5 years (2012-2016) oral cavity's oncology morbidity in Poltava region is represented in the work. There is a high prevalence of neglected tumors (45,3%) of this location together with significant amount of treatment refusal and 31.8 % 1-year mortality after diagnosis were established. 794 cases of oral cavity malignant neoplasms in Poltava region were registered during 2012-2016 yy. with 26.95 % from urban and 73.04% from rural areas. There are 174 (22.16 %) cases in females and 618 (77.84 %) cases in males were observed (male to female ratio is 3,5). Total 1-year mortality is 306 cases.

The first place in cancer structure is placed by cancer of lips - 355 people, the second one - cancer of the oral floor (147 cases). Other forms and unspecified parts of tongue - 96 cases, tongue – 75, palate – 67 and malignant neoplasm of gums - 54 cases.

KeyWords: morbidity, oncology, oral cavity, precancerous condition, malignant neoplasms.

INTRODUCTION

The article deals with the assessment of the incidence of oral malignancies in Poltava region for 4 years, from 2011 to 2015. There is a high incidence of neglected tumors of the named localization (it's about 31.8 %). Numerous refusals of treatment due to different circumstances were observed.

Malignant tumors are a major biomedical, social and economic problem not only in Ukraine but also in the world. The incidence and cancer mortality are steadily growing, increasing the risk due to the unstable economic situation in the country, unfavorable ecological situation and a significant aging of the population [1, 2].

The problem of cancer, especially malignant tumors is one of the most pressing in modern medicine. According to WHO, each year approximately 4.3 million people die from cancer in the world. Cancer is among the three leading causes of death in all the age groups over 50 years, both in the developed countries and in the developing ones [3, 4].

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Malignant tumors of the head and neck (excluding skin, eyes and brain) constitute about 5% of cancers in other locations. Cancer of the oral cavity and oropharynx ranks second among head and neck malignancies after cancer of the larynx, and their ratio is 2-10% of all human cancers.

However, this number of patients is considered significant because the disease results in an extremely severe dysfunction of breathing, swallowing, speech and appearance. The severity is primarily determined by the advanced and often incurable forms of disease, while advanced forms of cancer in other locations lead to death from certain metastases [5, 6, 7].

Combating malignant tumors is a major public health problem in Ukraine. The urgency of this issue is determined by the constantly growing incidence of malignant tumors in population, early diagnosis difficulties, high cost and difficulty of treatment, high disability and mortality rates.

Each year about 200,000 new cases of malignant tumors are registered in Ukraine.

Oncologic and epidemiologic situation in Ukraine and in some of the regions basing on long-term monitoring data is characterized by a continuous growth of cancer-related

morbidity. Thus, in 1980 the number of newly registered patients was 238.3 per 100,000 population and in 1996 this value reached 309.4, while in 2010 the incidence of malignant neoplasms in Ukraine amounted to 341.2 per 100,000 population. Each year cancer affects more than 160,000 people. This means that every day in Ukraine 442 new patients develop cancer or 18 cases per every hour. These figures indicate the intensity and magnitude of the problem. Each third or fourth man and every fifth or sixth woman has a risk of getting cancer within the lifespan [8].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

The aim of the article was to compare the incidence of oral malignancies in Poltava region in 2011-2015, identifying social-organizational problems of diagnosis and possible ways to improve them.

2.2 Subjects & Methods

The study involved the assessment of incidence of oral malignancies in Poltava region for the last 4 years (2011-2015) with the following locations: jaw, palate, tongue and other locations, such as lips and oral floor.

Conflict of interests
There is no conflict of interests.

3 RESULTS AND DISCUSSION

All cancer patients were divided into groups according to their age by the WHO classification (WHO classification, 1963): Group 1 – patients under 45 years; Group 2 – 45-59 years; Group 3 – 60-74 years; Group 4 – 75-89 years; Group 5 – over 90 years.

Jaw cancer. The total number of cases from 2010 to 2014 was 54 people (representing 6.8% of the total number of patients). The distribution by sex was as follows: 13 women and 41 men. The study showed that 26 people were diagnosed at stage III of the disease and 12 people at stage IV; 18 patients were registered in cities and 36 patients in villages; annual mortality rate was 39 people.

Neoplasms of the palate. The study involved the assessment of 67 cases for the period of 4 years, 8.438% of all the patients with cancer of the mouth, including 11 women and 56 men. Annual mortality was 38 deaths. In 24 patients cancer was diagnosed at the III stage and in 8 cases at stage IV. Of them 24 men lived in the city and 43 people lived in the village.

Tongue cancer. The total number of 75 patients (9.445%) attended Poltava Regional Oncology Center from 2010 to 2014. Only 14 of them received comprehensive treatment. Thus, 28 people received chemotherapy, 40 people underwent radiotherapy, 11 patients refused from any treatment for unknown reasons and 10 patients underwent surgical treatment. Furthermore, 43 people died within one year, 34 cases were diagnosed at stage III, and 13 at stage IV.

Lip cancer. The total number of patients with lip cancer for the entire period under investigation was 355 (44.72%); 256 men, 99 women; 274 patients lived in villages. Diagnosis was made at stage III in 81 patients, at stage IV in 41 patients; annual mortality rate was 64 cases.

Malignant tumors of the oral floor. The total number of people with this type of cancer from 2010 to 2014 was 147 cases (18.513%). Of them 94 were from villages, 53 people lived in cities. There were 141 men, 6 women; 93 patients were diagnosed at stage III, 21 patients at stage IV. Annual mortality rate was 69 cases.

4 CONCLUSIONS

The total number of patients with oral malignancies in Poltava region from 2010 to 2014 was 794. The quantity of urban residents was 214 (26.95%), rural residents – 580 (73.04%) patients (exceeding the number of city residents by 2.71-fold). All the patients were divided according to gender: 174 (22.16%) women, 618 (77.84%) men, which by 3.55-fold exceeds the number of women; annual mortality rate reached 306 cases. According to age the patients were divided as follows: Group 1 (45 years) - 8 people, Group 2 (45-59 years) - 160 cases, the highest number of cases was recorded in Group 3 (60-74 years) - 350 people, Group 4 (75-89 years) - 215 people, Group 5 (> 90 years) - 25 regis-

tered cases. Lip cancer affected the highest number of patients – 355 cases, cancer of the oral floor ranked second – 147 cases, other and unspecified parts of the tongue – 96 patients, tumors of the tongue – 75 patients. Besides, 67 people had palate cancer. The smallest number of cases was among the patients with jaw cancer – 54.

The doctors examining these patients did not pay adequate attention to the increased dry red border of the lips, desquamation of the epithelium, presence of sites without luster in the mouth, cracks or sores that bleed for a long time without healing. Facial nerve paresis was mistakenly taken for neurological disorders. Symptoms of mandibular malignancies were diagnosed as arthritis; bone destruction was taken for osteomyelitis. The absence of symptoms at early stages of oral malignancies is one of the unfavorable factors in the field of oncology.

It should be specifically emphasized that considering tense oncological situation in Ukraine, cancer diagnosis should be performed not only in oncological institutions, but in all the medical institutions including dental ones as well. Early diagnosis is the main factor determining the success of treatment and favorable prognosis in patients with oral malignancies.

Maxillofacial area can be easily examined both by a doctor and by the patient. However, cancer symptoms are sometimes so mild that the transition of chronic inflammatory or destructive process into malignant growth often goes unnoticed either by a specialist or the patient.

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