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The beautiful thing about learning is nobody can take it away from you—B. B. King

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RELATION BETWEEN TYPE 1 DIABETES MANAGEMENT AND INTERACTIVE DIABETES EDUCATION

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Background: Type 1 diabetes mellitus (T1DM) is the most widespread metabolic/endocrine condition among children/adolescents in Georgia. T1DM patients aged 0-18 yrs are treated both in- and outpatiently. In 2015-2019 totally 533 patients were hospitalized, 211 of them had fresh T1DM. Special attention is paid to interactive diabetes education (IDE) of patients/their caregivers that is very important for adequate diabetes management. IDE is initiated from the day of admission.

Aim: Our aim was to assess the effect of continuous, structured IDE on quality of metabolic control and acute complication incidence in children/adolescents with T1DM. Goals of IDE are - teaching about signs/symptoms, progression, acute complications (causes, signs/ symptoms, prevention and treatment) of T1DM; developing insulin injecting, self-monitoring/self-control skills (result interpretation; bread-units; physical activity, etc).

Methods: Patients treated/supervised at our Hospital were separated into 3 groups (Gr.): 211 patients with fresh T1DM (Gr.1); 150 patients with poor (Gr.2) and 361 patients with satisfactory (Gr.3) glycemia control. Following parameters: HbA1c, hyper-/hypoglycemic coma and ketoacidosis incidence, insulin doses were studied and compared before/after IDE course and psychologist counseling.

Results: Data obtained before IDE for Gr. 1, 2,3: HbA1c (%) - 13.5±2.1; 12.5±2.3; 7.0±2.5, respectively; hyperglycemic coma (%) – 17; 30; 5, respectively; ketoacidosis (%) – 78; 20; 0, respectively; hypoglycemic coma (%) -22; 35; 0, respectively; insulin doses (U/kg) – 1.7±0.1; 1.3±0.4; 0.7±0.4, respectively; QOL/Relation to Condition Questionnaire/RCQ (%) scores were 100; 80; 35, respectively. Post-education data: HbA1c (%) - 7.0±2.1; 8.0±2.2; 6.4±0.8, respectively; hyperglycemic coma (%) – 0; 4; 0, respectively; ketoacidosis (%) – 3; 8; 0, respectively; hypoglycemic coma (%) –0; 0; 0, respectively; insulin doses (U/kg) – 0.7±0.1; 0.9±0.4; 0.7±0.12, respectively; QOL/RCQ (%) scores – 95; 87; 97, respectively.

Conclusion: IDE, initiated at the moment of diagnosis, that lasts throughout in-hospital period, is regularly repeated out-patiently and tailored to individual patient needs gives knowledge, develops skills, creates motivation, helps to achieve good diabetes control, reduces and/or avoids acute complications and improves QOL of children and adolescents with T1DM. Lately the first book for children, adolescents and their caregivers “Diabetes Mellitus for Children and Adolescent“ was published in Georgian, it discusses all aspects of life with diabetes and management of the condition in a simple and attractive way. The book is delivered free of charge.

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CORRELATIONS BETWEEN GROUND-LEVEL OZONE CONCENTRATION AND COVID-19 CASES IN TBILISI

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We live in the midst of a global health crisis - a similar pandemic the world has not experienced for more than 100 years.

According to modern approaches, differentiation of solid dust particles into fractions, according to their aerodynamic diameter size are used to assess and normalize the impact on human health. Namely, PM10 (particles with an aerodynamic diameter of 10 μm) and PM2.5 (particles with an aerodynamic diameter of 2.5 μm). The latter are considered the most dangerous to health because they have the ability to penetrate into the peripheral areas of the bronchioles and prevent airway into the lungs. These are carbon monoxide, lead, nitrogen dioxide, particles (very small solid or liquid particles in the air), sulfur oxides, and ground ozone (ozone does not escape directly into the air but is formed by exposure to sunlight, nitrogen oxides, and volatile organic compounds. There are two categories of particles: 10 micrometers (μm) or less (1 μm = 10m6 meters) and 2.5 μm or less in size.

They adopt a 2030 emissions inventory that accounts for fully implementing anthropogenic emissions controls required by federal, state, and/or local policies, which is projected to strongly influence future ozone levels. We quantify a comprehensive suite of ozone-related mortality and morbidity impacts including emergency department visits, hospital admissions, acute respiratory symptoms, and lost school days, and estimate the economic value of these impacts. Both GCMs project average daily maximum temperature to increase by 1-4°C and 1-5 ppb increases in daily 8-hr maximum ozone at 2030, though each climate scenario produces ozone levels that vary greatly over space and time.

Near-term changes to the climate have the potential to greatly affect ground-level ozone. Using a 2030 emission inventory with regional climate fields downscaled from two general circulation models, we project mean temperature increases of 1 to 4°C and climate-driven mean daily 8-hr maximum ozone increases of 1-5 ppb, though each climate scenario produces ozone levels that vary significantly over space and time. These increased ozone levels are estimated to result in tens to thousands of ozone-related premature deaths and illnesses per year and an economic burden of hundreds of millions to tens of billions of U.S. dollars (2010$).

Air pollution, the release of various gases into the atmosphere, finely divided solids, or finely dispersed liquid aerosols at speeds that exceed the natural capacity of the environment to disperse and dilute or absorb them. O&NG emissions are predicted to affect surface ozone across a large geographical scale.[5]

Empirical assessment shows that ambient PM2.5, nitrogen dioxide, ozone, pressure, dew, Windgust, and windspeed increase the spread of COVID-19, high relative humidity and ambient temperature have mitigation effect on COVID-19.

Methods: For several years now, we have been conducting between the troposphere (surface) ozone level and the incidence of various non-infectious-infectious diseases in Tbilisi. Given the current

unorthodox situation, when the Covid-Pandemic swept through all aspects of our lives, we wondered if we could judge the frequency of Covid-pandemics and the relationship between ozone and the troposphere ozone. We conducted an epidemiological study between the troposphere ozone level and the frequency of co-infected cases in Tbilisi.
The study was conducted with a German-made ozonometer at a frequency of three to three minutes, every hour , in the Vake-Saburtalo district of Tbilisi, every day, continuously. Here is the material on how the frequency of co-infection cases in Tbilisi varied by months.
Correlations were determined by Spearman correlation analysis using the statistical package SPSS-23

Results: The first study showed that there was a reliable correlation between ozone level and coovid-19 morbidity ($p < 0.05$)
However, to draw final conclusions at this stage is impossible. The issue is still under investigation. determine the interesting result - the level of covidination decreases when the ozone level of the troposphere decreases too.
However, to draw final conclusions at this stage is impossible. The issue is still under investigation.

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BIOLOGIC AGENTS ROLE IN THE TREATMENTS OF PSORIASIS: UPDATE FOR THE CLINICIANS

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ABSTRACT

The biologic agents within the past two decades has dramaticallyimproved the treatment of psoriasis and psoriatic arthritis. Given that there now exists 11FDA approved biologic options available for psoriasis, with more in the pipeline, the therapeutic armamentarium has been greatly enhanced. However, the fact that there are somany available options has also caused confusion for providers. Therefore, this manuscript deliberately focuses on the most clinically useful facts (such as efficacy and safety data) about each and every FDA approved biologic agent (including pipeline agents) for psoriasis.

Keywords: biologic therapy, psoriasis, IL-17, TNF-alpha,

Introduction: The great progress has been made with biologic therapy for psoriasis in terms of both the safety and efficacy of these agents. This new treatment paradigm was made possible by the continually advancing knowledge of the pathophysiology of psoriasis. Thirty years ago, psoriasis was still primarily considered a problem with the hyperproliferation of the epidermis [1]. Recent research into the pathophysiology of psoriasis has highlighted the importance of the immune system in this disease. There now exists a clear mechanism, down to the molecular level, regarding which cytokines are implicated in the pathophysiology of psoriatic disease. In the initial cascade of psoriasis pathophysiology, a variety of cell types are involved which include keratinocytes, natural killer T cells, plasmacytoid dendritic cells and macrophages. These cells secrete cytokines which activate myeloid dendritic cells and in turn, activated myeloid dendritic cells secrete IL-12 and IL-23. Both of these cytokines are integral in the cellular cascade of psoriasis pathophysiology [2]. IL-12 causes differentiation of native T cells to Th1 cells (which produce IFN-γ and TNF-α) and IL-23 is important for the proliferation of Th17 and Th22 cells. Th17 cells produce IL-17, IL-22 and TNF-α1 When considering all of these different signaling pathways, IL-23 [3] mediated activated of the Th17 pathway is hypothesized to be the main contributor to the inflammation seen in psoriasis.2 Given that the IL- 17 and IL-23 biologic agents are more effective may demonstrate the fact that these pathways are more [4]. In the pathophysiology of psoriasis and that psoriasis patients may, on the whole, exhibit more pathology in this specific pathway. The fact that biologic agents interact with a specific cytokine (such as TNF-α, IL-17 or IL-23) in a targeted manner has revolutionized the capacity to treat psoriasis [5] compared to the era of a more generalized immunosuppression reflected by the traditional oral medications. This represents an improved treatment regimen where targeted immunomodulation has resulted in a great enhancement in both safety and efficacy for biologic agents [6].

Methodology: The goal of this manuscript is to aid the busy practicing dermatologist in becoming more adept at using these agents with the ultimate aim of improving patient care. Each biologic agent will be presented according to the class that itbelongs, we will discuss each of tem separately:

A. TNF-Alpha Agents/ Etanercept (Enbrel®) Etanercept is a recombinant human TNF-α receptor protein fused with the Fc portion of IgG1 that binds to soluble and membrane bound TNF-α and to tumor necrosis factor-β.3 It is currently approved for treatment of moderate-to-severe adult and pediatric plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis [7]. Adalimumab (Humira®) Adalimumab is a recombinant, fully human, monoclonal antibody against TNF-alpha that blocks the interaction of TNF with both of its cell-surface receptors, with high affinity and specificity. For over 20 years, adalimumab has been used worldwide in more than 1 million patients for 10 different indications which are: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa and uveitis [8]. Certolizumab Pegol (Cimzia®) Certolizumab (CZP) is a monovalent, humanized Fab antibody fragment, conjugated to a polyethylene glycol (PEG) that inhibits TNF-alpha in a dose-dependent manner. This gives CZP a unique structure amongst all other biologics. There are 6 indications: Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and moderate-to- severe plaque psoriasis [9]. Infliximab (Remicade®) Infliximab is a chimeric monoclonal antibody comprised of a mouse variable region and a human IgG1-alpha constant region which exerts its neutralizing action by binding to both soluble and transmembrane TNF-alpha molecules. It is approved in adults for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis [10]. B. IL 12/23 Agents/Ustekinumab (Stelara®) Ustekinumab is a human monoclonal antibody that binds with high specificity and affinity to the p40 subunit of both interleukin 12 (IL-12) and IL-23, and as a result, suppresses bothmIL-12 and IL-23 mediated inflammation which causes psoriasis. C. IL-17 Agents/Brodalumab (Siliq®) Brodalumab is a human monoclonal antibody that binds the IL-17 receptor A and blocks the biologic activities of IL-17A, IL-17F, IL-17A/F and IL-17E (also known as IL-25). This is a unique mechanism of action as it is the only biologic in its class which blocks the entire IL-17 receptor. It is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients. Secukinumab (Cosentyx®) Secukinumab is a fully human G1k monoclonal antibody, which selectively binds and inhibits IL-17A.22 It is currently FDA approved for plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, and active non-radiographic axial spondyloarthritis. Ixekizumab (Taltz®)is a high-affinity, humanized IgG4 monoclonal antibody for IL-17A, inhibiting interaction with the IL-17 receptor. FDA indications for ixekizumab include plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis. Bimekizumab is a novel IgG monoclonal antibody that binds to a peptide region that is shared by IL-17A and IL-17F. D. IL-23 Agents/Tildrakizumab (Ilumya®) is a humanized IgG1, monoclonal antibody designed to selectively block IL-23 by binding to the p19 subunit. Risankizumab (Skyrizi®) is a humanized IgG1 monoclonal antibody selectively targeting the p19 subunit of IL-23. Guselkumab is a fully human IgG1λ monoclonal antibody which inhibits the p19 subunit of interleukin 23 (IL-23). FDA approved indications for guselkumab include moderate-to-severe plaque psoriasis and psoriatic arthritis.

Discussion: Our manuscript reviews the most relevant facts about every biologic agent available for the treatment of psoriasis with a special focus on the merits and demerits of each agent. After reviewing all the available options, it has become clear that each of these agents has their own unique merits. Therefore, the more simplistic idea that several of the older The recommendation of the authors is not to dismiss any biologic agents currently available based on just superficial

assessments or a cursory glance. The authors hope that this complete characterization of all the biologic agents used by dermatologists for psoriasis proves helpful in understanding the nuanced differences between the agents, which could prove to be very important in improving patient care and patient satisfaction

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EPIDERMOLYSIS BULLOSA AND STEM CELL THERAPY

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ABSTRACT

The main goal of regeneration or sustained genetic correction of damaged tissue, advanced tissue-engineering techniques are especially applicable for many dermatological diseases including wound healing, genodermatoses (like the severe blistering disorder epidermolysis bullosa) and chronic (auto-)inflammatory diseases. This review summarizes general aspects as well as current and future perspectives of stem cell therapy in dermatology.
Keywords: Epidermolysis bullosa, Bone-marrow transplantation, MSC-cell therapies.

Introduction: Stem cells (SCs), common to all multicellular organisms, are specified as undifferentiated self-replicating cells possessing the ability to generate, sustain and replace terminally differentiated cells. They show two key features: self-renewal (cell divisions with maintenance of the undifferentiated state), and capability of in vivo and in vitro reconstitution of a given tissue via differentiation into specialized cell types1. SCs are commonly subdivided into two main entities, embryonic stem cells (ESCs) (pluripotent) and adult SCs (multipotent or unipotent).

Methodology: 1. MSC-cell therapies SC therapies are increasingly established in the experimental treatment of genetic diseases, recently also in patients with recessive dystrophic EB (RDEB), a rare genetic blistering disease. RDEB patients lack genes for synthesis of Collagen VII. These symptoms mainly account for more severe disease complications, such as mitten deformities of hands and feet and aggressive epithelial cancers.Therapeutic approaches, either with intravenous infusion or direct local administration of MSCs to chronic wounds have started however, to provide novel insight into key BM cells and mechanisms germane to repair and regeneration of the epithelium. Initially, intradermal injections of human BM-MSCs showed a dose-dependent, significant higher production and in loco deposition of type VII collagen associated with restoration of immature anchoring fibrils and superior dermal-epidermal integrity compared to controls with intradermal phosphate-buffered saline-injections in DEB mouse models. In line with this preclinical data, Conget et al.126 described the replenishment of type VII collagen at the dermal–epidermal junction upon intradermal BM-MSC injection provided from healthy donors into chronic wounds of two RDEB individuals3. The administration led to a reduced blister formation (up to 6 months) and an increased reepithelialisation of chronic ulcers. Tissue remodeling activity of the transplanted MSCs, owing to both, their integration into the skin and their secretion of growth factors and cytokines participating in the regulation of tissue regeneration, might activate self-healing mechanisms in RDEB skin. Subsequent studies questioned a predominant impact of SC on phenotypic amelioration 1. Petrof et al.10 showed that a single intradermal injection of allogeneic fibroblasts accelerated the initial rate of wound healing in patients with RDEB within the first 28 days although this effect diminished thereafter. In another study, both the injection of allogeneic cultured fibroblasts in suspension solution as well as of the suspension solution alone led to a similar increase in type VII collagen

expression and improved wound healing in chronic non-healing ulcers of RDEB patients, independently of type VII collagen regeneration The mechanical stimulus in the course of intradermal injection itself was thus supposed as a potential cause of improved wound healing, reflecting an elevated expression of heparin binding-EGF-like growth factor in response to subclinical inflammations that occur after injections into the human skin. Providing a clinically feasible approach of systemic treatment, also the infusion of allogeneic BM-derived SCs led to a phenotypic improvement in RDEB patients, showing reduced blistering and tissue fragility 2. Transplanted SCs from healthy donors are believed to engraft into the skin, differentiate to fibroblasts and keratinocytes, synthesize the missing type VII collagen anchoring fibers and thereby improve the fragile skin and shearing off of the epidermis63. In this respect, it has been shown that low levels of restored expressions of collagen VII (below 30%) are sufficient to significantly improve the RDEB phenotype and even a correction of about 3% COL7A1 mRNA seemed to be adequate for phenotypic reversion in a mouse model. Ten RDEB children who received systemic (intravenous) allogeneic (wild-type) BM-MSCs showed improved wound healing, reduced skin redness, a subjective improvement in quality of life and high tolerability. As skin biopsies at 2 months post-treatment revealed no increase in type VII collagen nor new anchoring fibrils, phenotypic improvement possibly reflected a predominant immune suppressive and immune modulating effect of MSCs 11. In another study with RDEB patients fewer blistering and significantly shortened healing time after treatment with BM-MSCs was demonstrated, either with or without concomitant cyclosporine 12. In this cohort, electron microscopic examination additionally confirmed an increase in anchoring fibrils after treatment. In summary, intradermal or intravenous injections of MSCs have shown some clinical benefits for RDEB patients. However, feasible application techniques as well as optimal cell dosage and frequency schedules for administration of allogeneic MSCs still have to be established and evaluated in future clinical trials. Further, biological and pratical limitations, like the ephemerality of the transplanted cells and potential immune rejection towards neo-antigens hitherto hinder the clinical applicability.

2) Bone-marrow transplantation Following the demonstration of successful BM SC transplantation in murine RDEB, a clinical trial of whole BMT was performed in children with RDEB13. The first step included a high-dose chemotherapy to immunoablate patients to ensure more dependable lymphohematopoietic engraftment. Unfiltered cell populations of the donor BM were used based on previous observations that both hematopoietic and mesenchymal BM-derivedSCs have the potential to increase the production of C7134. All six patients, who underwent BMT had some clinical improvement and five of the six showed increased C7 at the DEJ at the time biopsies where taken between day 100 and 200. Three of the six individuals showed an immense clinical improvement, with a reduction from 50% blistering area of the body surface to less than 10%. The remaining three patients exhibited a moderate improvement with less than 25% of the body surface area affected 4. However, toxicities occurred, as one patient died before the BMT due to heart failure possibly related to cyclophosphamide toxicity and pre-existing renal failure. Another individual died 6 months after transplantation because of an infection related to graft failure. Therefore, BMT protocols are currently refined by considering the use of reduced intensity conditioning and targeting of distinct subpopulations of BM cells.

3) Gene therapy A low worldwide incidence of rare (or “orphan”) genetic skin diseases limits the accrual of data for research and suspends advancements in developing therapeutic concepts for these skin conditions. But since all of the most devastating forms of such inherited skin diseases like

EB are mostly resulting from monogenic defects, in theory, their remediation at the genetic level should be more feasible 5. Sustained gene correction of continuously renewing tissue like skin, however, relies on the efficient molecular targeting of SCs.

A proof-of-principle study with somatic gene therapy in EB has been published 14. Via a retroviral vector, a LAMB3 transgene has been inserted into autologous keratinocytes that were then grafted back as a confluent sheet onto the thigh of an adult patient with generalized intermediate junctional EB. In the following years, the graft has continued to express laminin-332 at the dermoepidermal junction, leading to a clinical improvement and long-term epidermal stability. This remarkable benefit was achieved although the number of holoclone SCs was reduced in the patient, probably a repercussion of long-term skin blistering resulting in niche destruction and SC depletion or exhaustion. In the future, optimized protocols, with the goal to effectively isolate a sufficient amount of autologous EpSC, before being corrected by gene transfer, might facilitate the procedure9. These cells, after building grafts and being transplanted, have the potential to induce long-term (if not permanent) regeneration of wounded skin. So far, promising observations of the use of genetically corrected skin grafts include (1) a total engraftment, yielding a morphologically and functionally normal, non-blistering skin that is able to resist mechanical stress, (2) continuing laminin beta-3-protein and laminin 332 expression that consequently strengthens the epidermal-dermal junction over a period of at least 8 years, (3) the ability to persistently and effectively restore the epidermis with only a few transgenic EpSC, which accounted only for a small subpopulation of transduced cells (most transduced keratinoctes have been shorter-living transit-amplifying progenitors) 10. With regard to hitherto limited and/or transient efficacy as well as safety/tolerability issues, optimal therapy for EB is doubtful to involve justllogeneic cells. More promise may hold a combination of gene, protein, drug, and cell therapies 6.

4) iPSCs iPSCs therapies are therapeutically promising for genetic skin disease, because they can be rather easily exploited to be genetically manipulated. In addition, this approach makes modeling of skin diseases via targeted mutagenesis of the relevant genes possible forgoing the usage of ESCs15. The successful establishment of iPSC-based therapies for hereditary skin diseases mainly relies on four steps: First, via a patient's skin biopsy cells have to be isolated. Second, these cells have to be transformed into iPSCs via genetic reprogramming. Third, genetic aberrations in obtained iPSCs have to be (safely) corrected, preferably through homologous recombination (HR) 7.

In cell culture models, successfully generated iPSc from either gene corrected (autologous) RDEB fibroblasts or healthy (allogenic) individuals are able to differentiate into hematopoietic SCs and MSCs that can home to mucocutaneous blistering areas where they differentiate into keratinocytes and fibroblasts69, 8. Additionally, autologous grafting of in vitro generated 3-dimensional (3D) skin equivalents by iPSCs shows generation of stratified epidermis in vitro and in vivo (animal models). The first attempt to use revertant cell therapy in an individual with generalized intermediate junctional EB yielded no functional benefits after (successful) grafting of isolated revertant keratinocytes, which were expanded to epidermal sheets. Of note, cultured keratinocytes showed 30% reversion, whereas the number of reverted keratinocytes dropped to 3% in the graft, probably becauseof lacking holoclones15. An alternative approach using punch graft transplantation of revertant skin, however, has been used successfully to heal chronic erosions with enhanced expression of laminin-332 in a patient with a similar form of junctional EB and mutated LAMB3 gene. The improved skin integrity was maintained for at least 18 months.The future impact of this

approach thus relies on methods to more efficiently expand revertant keratinocytes in culture and to generate grafts containing adequate numbers of revertant SC to yield functional repair and regeneration of the skin.

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GENETIC INVESTIGATIONS - MODERN PREVENTIVE HEALTHCARE DIRECTIONS IN OCCUPATIONAL MEDICINE

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ABSTRACT

The nature and structure of occupational pathologies have changed significantly in the face of the rapid and steady growth of the use of chemical compounds in many industries. Health disorders developed by chemical compounds are apparently dependent on their concentrations and exposure in enterprise settings. High chemical concentrations cause acute and chronic intoxications, while low concentrations reveal allergen properties and lead to the development of occupational allergic diseases. In modern occupational medicine, great importance is attached to the study of hereditary factors. The identification of individuals who may develop occupational diseases in general, and occupational allergic diseases in particular, has acquired the most practical significance. The involvement of genetic research in the complex of secondary prevention measures used in occupational medicine, in particular during preliminary and periodic medical examinations, in the form of HLA-system antigens, the proposed method of which facilitates research, avoids the risk of developing manganese-based occupational bronchial asthma and formation of invalid forms.
Keywords: occupational medicine, occupational bronchial asthma caused by manganese, secondary prevention, genetic research.

The steady growth of industry and scientific and technical progress create opportunities for the emergence of new professions as well as new enterprise factors. This contributes to the increase in the incidence of certain forms of occupational diseases and the emergence of new occupational pathologies. The nature and structure of occupational pathologies have changed significantly in the face of the rapid and steady growth of the use of chemical compounds in many industries. Health disorders developed by chemical compounds are apparently dependent on their concentrations and exposure in enterprise settings.

High chemical concentrations cause acute and chronic intoxications, while low concentrations reveal allergen properties and lead to the development of occupational allergic diseases. Despite the reduction of dust pollution and gaseous pollution in enterprises, the exposure to the sensitizing effects of chemical compounds has been increased, including the frequency of its most severe forms - occupational bronchial asthma. Consequently, the development of occupational allergy prevention methods and implantation in practice has acquired special importance.

Among the occupational respiratory allergic diseases, occupational bronchial asthma occupies second place in the Structure of Occupational Diseases of Georgia, after the vibration disease. Consequently, the introduction of new directions for the prevention of occupational bronchial asthma will reduce the incidence of the disease as well as the development of invasive forms.

In modern clinical medicine, great importance is attached to the study of hereditary factors. The importance of hereditary predisposition to non-occupational allergic diseases is not in doubt (1,2). Hereditary load is undoubtedly important in the complex action of environmental factors, including leading environmental factors - chemical, physical and biological, as hereditary background

determines the body's response, specific subclinical changes in employees, and the possibility of disease development.

The importance of hereditary load in the development of occupational allergic diseases is controversial and there are conflicting opinions based on the studies conducted (2, 12, 7). Some of the authors recognize the role of inheritance in the development of occupational disease, but also note that it is not given leading importance (5).

In occupational medicine, the identification of individuals who may develop occupational diseases in general, and occupational allergic diseases in particular, has acquired the most practical significance.

From this point of view, it is interesting to study human leukocyte antigens (HLA) in various pathologies, as these antigens are relatively easy-to-determine genetic markers, and the system polymorphism reflects the variety of all possible combinations encountered in the human population (9).

Studies in this area have been conducted in rheumatology, hematology, endocrinology, etc. (4,10,11). There are also numerous studies on the correlation of HLA-system antigens with respiratory allergic diseases (6, 3, 14). In addition to increasing the frequency of HLA-system antigens, the researchers point to the decrease in the frequency of individual antigens (13). Also, the data on the association of HLA-system antigens with disease severity, age, sex, provoking factors (cold air, stress, intercurrent infection) differ. Some authors do not find such an association at all (1), others - note a positive correlation (13).

Under the influence of manganese compounds, the employees in Zestaponi and Chiatura who were diagnosed with developed occupational allergic diseases, in particular bronchial asthma, underwent the determination of the major histocompatibility complex antigens (MHC) using Terasaki and McClelland the standard two-stage MicrolymphocytotoxicityTest (1). Standard panels of anti-HLA serums were used. Each antigen was tested with at least three monospecific antiserums. Genetic research has shown that occupational bronchial asthma is characterized by a positive or negative association with different genetic markers of the disease. In particular, positive correlation was found between B12 antigen (RR=3.0), A9A28 (RR=4.95) phenotype and A2B35 (RR=6.3), A9B12 (RR=4.9), A28B13 (RR=16.03) haplotypes, and negative - B16 (RR=0.21), B27 (RR=0.12), cw3 (RR=0.43) antigens, B7B17 (RR=0.22) phenotype and A2B16 (RR=0.06), A9B21 (RR=0.07), A10B17 (RR=0.06) haplotypes.

Thus, manganese-induced occupational bronchial asthma is characterized by the following immunogenetic markers: type B12, B13, B35 antigens and the pheno- and haplotypes that contain them. It has also been shown that aggravation of the disease course is expected in individuals with occupational bronchial asthma who develop type B41 antigen.

An important part in the development of atopic, occupational bronchial asthma is played by the sensitizing properties of the industrial allergens, the intensity, and duration of exposure, the physicochemical properties and, no less important, the immunogenetic characteristics of the organism in contact with the allergen.

The involvement of genetic research in the complex of secondary prevention measures used in occupational medicine, in particular during preliminary and periodic medical examinations, in the form of HLA-system antigens, the proposed method of which facilitates research, avoids the risk of developing manganese-based occupational bronchial asthma and formation of invalid forms.

The facilitation of the genetic investigation in identifying the mechanisms for the development of occupational diseases will create a new direction of prevention in Occupational Medicine.

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IMMUNOGENETIC MECHANISMS OF OCCUPATIONAL ALLERGIC DISEASES

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The directions for the prevention of occupational pathologies in employed populations are being developed based on scientific achievements and medical research. Therefore, it is important to implement the research results into practice and to include them in the scheme of primary and secondary preventive measures. The immunological status of occupational allergic pathologies was identified in clinically confirmed cases of bronchial asthma and allergic dermatitis caused by manganese compounds. The studies have revealed some patterns that characterize occupational allergies caused by manganese compounds as industrial harmful factors. We believe that the established changes that can be used during periodic medical examinations and the practice should be used for making early diagnosis of the diseases to prevent severe and disabling forms of the diseases.

Keywords: occupational medicine, manganese, bronchial asthma, dermatitis, immunologic changes.

In recent years, the use of chemical compounds has been increased both in everyday life as well as in manufacturing processes. Consequently, as the area of their impact on the population in general and the employed population, in particular, is increasing, the number of cases and manifestations of various health problems in the population is increasing as well.

In the recent decade, a growing trend of allergic diseases has been observed in Georgia. In particular, the number of new cases of bronchial asthma has been steadily increasing: in 2008 - 3189 cases, in 2010 - 3285, in 2015 - 3261 cases, and in 2019 the total prevalence of cases with asthma and asthmatic status registered in Georgia equals to 286.7 and the incidence rate - 59 [1].

Simultaneously, the number of such cases is increasing in the employed population. Among the leading causes of allergic diseases appear chemical compounds.

Individuals exposed to chemical compounds may develop both their own occupational and conditional occupational pathologies (both diseases and intoxications). However, in recent years, under the background of the increase of allergic cases in the population in general, the pathologies have developed as a result of the sensitization to chemical compounds, in particular, allergic diseases of the respiratory system - occupational bronchial asthma and asthmatic bronchitis, as well as allergic skin diseases.

The directions for the prevention of occupational pathologies in employed populations are being developed based on scientific achievements and medical research. Therefore, it is important to implement the research results into practice and to include them in the scheme of primary and secondary preventive measures.

Respiratory system pathologies take a leading position in the structure of occupational diseases in Georgia, while allergic diseases of the respiratory system, in particular occupational bronchial asthma, take the second most common place after the vibration disease; while occupational skin pathology is the fifth on the list, almost half of them (48.6%) appear to be contact dermatitis, 27.8% - occupational eczema, and 19.7% - allergic dermatitis.

It should also be noted that in addition to the exposure to the production factor itself (in this case a chemical compound), other risk factors should also be considered, which are no less important in the development of the disease as they accelerate the onset of the disease or aggravate its course. Such risk factors include hereditary predisposition, tobacco consumption, nutritional characteristics, and environmental factors, including the living environment.

The identification and consideration of these factors in the diagnosis of occupational pathology is very important, besides, it is essential to include measures against them in the complex preventive actions [3].

The Department of Environmental Health and Occupational Medicine has been conducting complex hygienic, occupational pathology and immunological researches in the mining and mineral processing enterprises for years: in Chiatura and Zestaponi enterprises, Racha arsenic extraction and processing enterprises, Rustavi chemical and concrete plants, etc. Occupational allergological pathology was identified, however, immunologic studies were conducted only in the employees of Chiatura and Zestaponi. The immunological status of occupational allergic pathologies was identified in clinically confirmed cases of bronchial asthma and allergic dermatitis caused by manganese compounds.

Skin application test and provocative inhalation test with 20% manganese chloride solution were performed in employees diagnosed with occupational respiratory allergies (occupational manganese-induced asthma, asthmatic bronchitis). Immunological studies included the study of T- and B-lymphocytes by the Jondal (1972) method, the determination of T-suppressors and T-helpers (by sensitivity to theophylline), including the determination of the ratio (immunoregulation index), determination of G, A, and M class immunoglobulins (by Manchini method of radial immunodiffusion in gel, 1965), determination of total E-immunoglobulin by radioimmunosorbent test (RIST) Will (1973) [2,4,5] method.

For the first time in the Georgian population, it has been established that manganese-induced occupational bronchial asthma is characterized by certain features of immunological shifts. In particular, under the background of decreased number of T-lymphocytes, the ratio of helper and suppressor T-lymphocytes subpopulation was changed (decreased immunoregulatory index 1.43, norm - 2.42, $P<0.01$), the level of B-lymphocytes was maintained; Dysimmunoglobulinemia is present: G and A-class immunoglobulins are sharply reduced, the total number of E-immunoglobulin is increased, and M-immunoglobulin remains within the normal range. This gives us reason to conclude that manganese-induced occupational bronchial asthma is accompanied by pronounced disorders of immune homeostasis involving predominantly immunopathological processes. The disease can be attributed to the group of current bronchial asthma with E-conditions, the type of atopic bronchial asthma.

Along with the manganese-compound-induced occupational bronchial asthma occupational pathology of the skin has also been revealed; such kind of study was first to be carried out in Georgia. The research has revealed certain features of immunological shifts in the patients with manganese-induced allergic dermatitis (30 cases) and manganese-induced eczema (20 cases). The control group comprised healthy individuals. Special attention was paid to the peculiarities of occupational dermatoses, etiological factors, and clinical course.

The survey of the employees of Zestaponi enterprise was conducted using a special questionnaire, during the allergological examination the existence of exposure, elimination, and re-exposure syndromes were being identified; Skin application test was performed with 20% manganese chloride solution, as well as skin tests with household, plant and infectious allergens. Several

parameters were determined in the immunological studies: β- and γ-interferon index, phagocytic index, content of T-lymphocytes and its subpopulations (helpers and suppressors), immunoregulatory index, B-lymphocyte levels, G, A, and M immunoglobulin levels.

It has been established that during occupational dermatoses depression of both cellular and humoral immunity occurs: the interferon system is suppressed, the number of T-helpers, the immunoregulatory index, the level of B-lymphocytes, the levels of G, A, and M immunoglobulins are reduced. Indicators of phagocytic activity of the organism are also reduced.

It is conceivable that the changes observed in manganese-induced dermatoses are due to the sensitizing and intoxicating effects caused by the action of manganese compounds in the form of enterprise poisons and metal-allergens.

The studies have revealed some patterns that characterize occupational allergies caused by manganese compounds as industrial harmful factors. We believe that the established changes that can be used during periodic medical examinations and the practice should be used for making early diagnosis of the diseases to prevent severe and disabling forms of the diseases.

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MELANOCYTIC DISEASES

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ABSTRACT

It was traditionally assumed that cancer cells of melanoma arise from melanocytes. Recently, however, a hypothesis was posed that melanoma could also descend in extrafollicular SCs altered by harming factors such as ultraviolet (UV) A and UVB 5. Experimental studies are currently ongoing to investigate the mechanisms capable of causing damage to the DNA of SCs, as to ascertain this hypothesis
Keywords: Melanocytic diseases, Melanocyte development, Melanoma.

Introduction: McSCs are essential to maintain melanocyte populations in human skin and its appendages. Studies on McSCs have elucidated molecular mechanisms underlying ordinary melanocytic development as well as melanocyte-related pathological conditions like vitiligo and melanoma, although still many questions regarding the characterization of McSCs remain unsolved 3. . Human iPSCs may be useful for the characterization of human McSCs, since this application allows the acquirement of a sufficient amount of patient-specific melanocytes along the differentiation of iPSCs. These cells could then be applies for disease modeling and evaluation of potentially therapeutic approaches156. The use of HSCs transplantation, adjuvant to chemotherapy and immunotherapy for patients with metastatic melanoma, has been already evaluated in clinical trials. These strategies should allow the use of increased chemotherapy doses for more efficient eradication of tumor cells. However, definitive results are still missing A distinct type of pluripotent, non-tumorigenic (in vivo) MSCs refer to the term multilineage-differentiating stress-enduring cells (Muse cells). These cells can be conveniently obtained from mesenchymal tissues (such as dermis and bone marrow) and human mesenchymal cultured cells (such as dermal fibroblasts). After culturing in a specific differentiation medium containing ten factors (Wnt3a, stem cell factor, endothelin-3, basic fibroblast growth factor, linoleic acid, cholera toxin, L-ascorbic acid, 12-O-tetradecanoyl-phorbol 13-acetate, insulin–transferrin–selenium, and dexamethasone), Muse cells derived from dermal fibroblasts have been shown to readily transform into functional melanocytes 2. These differentiated Muse cells expressed melanocytic markers, grew in 3D cultured skin and produced melanin after transplantation to the back skin of immunodeficient mice 1. However, in contrast to other pSCs such as ES cells and iPS cells, Muse cells show low telomerase activity and are not able to grow tumors in vivo. This technique might be the basis for new treatment approaches to melanocytic diseases like vitiligo.

Methodology: 1) Cancer stem cells Several years ago, it was discovered that a small sub-population of acute myeloid leukemia cells could reestablish tumors in severe combined immunodeficiency mice, while the vast majority of the tumor cells could not 5. This study underlies the cancer SC hypothesis, which implicates that cancer SCs have characteristics comparable to the SC population of their tissue of origin (i.e., self-renewal, differentiation potential) 6. They are assumable very rare

within the tumor and are thought to produce progenitor cells that can generate all types of cells comprising the tumor. CSCs pose a challenge for cancer therapies, because eradicating the bulk tumor usually does not include all CSCs, leaving enough of them at liberty to re-establish the complete heterogeneity of cancer tissue. In addition, these SCs might be more resistant to chemotherapy, and even targeted molecular therapies via their relatively high expression of the multi-drug resistance genes (e.g., MDR-1, BRCP1), a common feature of many SCs. Furthermore, owing to their ability to rapidly induce DNA repair mechanisms, CSCs are often highly resistant to radiation therapy. Finally, they appear to be particularly adept in stimulating angiogenesis, nurturing tumor development CSCs can switch between quiescence (tumor dormancy) and active cell division with subsequent varying chemosensitivity, a behavior that mainly depends on changes in the microenvironmental niche and involves complex signaling pathways regulating tumorigenic growth and dormant arrest 10. CSCs further possess the capability to create new niches during the metastatic process160,161. These “metastatic niches” are defined by specific locations (e.g., metastatic cells occupying native SC and perivascular niches), signaling pathways (e.g., PI3K-AKT pathway as a critical survival input for metastatic cancer cells), incorporated stromal (e.g., endothelial) cell types and ECM proteins (e.g., tenascin C which strongly promotes SC functions). The components of this micromilieu support the survival, self-renewal and expansion of disseminated metastatic CSCs. Beside melanocytic SCs or melanoma cancer SCs probably involved in the pathogenesis of melanoma, CSCs have also been demonstrated in non-melanoma skin cancer such as squamous cell carcinoma (SCC) in mice. The proliferation and expansion of these CSCs are markedly influenced by their ability to respond to TGF-β receptor II and integrin/focal adhesion kinase-mediated signaling at the tumor–stroma interface. This pathway is crucially important in human cancer 6. It acts initially tumor suppressive (inhibition of proliferation) but promotes metastasis in later stages in response to a tumor associated altered cellular context and variable environmental signaling profiles. Studies have revealed that several distinct CSC populations coexist in SCC and that tumor initiation and metastatic potential of these populations can be uncoupled 7. Therefor understanding CSC biology it is critical to develop novel CSC-targeted therapies, especially for patients with cancer and a poor prognosisNew therapeutics may be designed to specifically target these cells to block cancer progression. At the moment many chemotherapeutics attack rapidly dividing cells, so that it is easy for slowly dividing cancer SCs to evade these therapies40. Whether skin tumors like melanoma follow a cancer SC model for tumor development or a hierarchical model of tumor growth and progression (or combinatory/ other models) remains to be determined. These features of tumor dynamics, however, have implications on drug development in order to increase the efficacy of CSCs targeting 9. Cancer SCs from solid tumors usually express organ-specific markers. However, many caveats impede the discovery and identification of cancer SC markers for diagnostic and therapeutic purposes, to include the potential that the expression of these cell surface markers is not stable, that daughter cells may express different markers, that markers may not be unique to the cancer SCs but expressed in other cell types as well and that these surface protein markers may not have any role in cancer SC biology 8. Beside the isolation of CSCs by flow cytometry according to CSC-specific cell surface markers, CSCs can be identified by so-called “side population chains (SP)” within a tumor. The latters refer to a subpopulation of tumor cells that is highly conserved in human cancer cell lines and linked to SC characteristics (clonogenic). It further features drug transport property with multidrug resistance and might serve as a “evolutionary backup” to keep alive at least a sub-fraction of cells when exposure to cytotoxic compounds occurs. SP show differential efflux activity to the main cell

population usually measured by efflux of the fluorescent DNA binding dye Hoechst 3334. Moreover, CSCs may be determined through sphere assays, since tumorigenic cells showing SC characteristics have the ability to grow as floating spheres in serum-free medium The significant role of aberrant Wnt signaling in cancer and CSC has engendered substantial efforts into the development of therapeutic approaches to target this pathway 9. Several small molecules, involved in tumor signaling, have been identified that selectively block the p300/β-catenin interaction, thereby increasing the CBP/β-catenin interaction, which maintains long-term pluripotency in a variety of SC populations. Thus the therapeutic potential of CBP/β-catenin antagonists (e.g., ICG-001) has been studied in various preclinical tumor models, where it has demonstrated the ability to safely eliminate drug-resistant tumor-initiating cells.

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STEM CELL NICHES AND SKIN DISORDERS

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ABSTRACT

Skin SCs reside in specialized morphological and functional units with a specific microenvironment. These so-called niches may contain various SCs as well as supportive cells providing framework or signaling to the SCs. Within human skin, at least five different niches have been delineated (basal layer of the epidermis, HF bulge, base of sebaceous gland, dermal papillae and dermis), that harbor different types of skin SCs:
Keywords: Stem Cells, Dermal niches, Skin.

Introduction: a) Interfollicular epidermal SCs are scattered singly across the dermal-epidermal junction. In the mucosa and on the palms and soles, SCs are located at the base of the rete ridges. They constitute about 1%~7% of epidermal basal cells. Several human SC markers have been described, including high surface expression of α6 and β1 integrins that may be relevant for sustaining the attachment of epidermal SC to their basement membrane through hemidesmosomes 1. Progenies from epidermal SCs that withdraw from the cell cycle, show a suppression of integrin α6 expression, before they start differentiating and moving towards the skin surface, where they slough off along terminal differentiation after approximately 4 weeks33. Furthermore, p63 (a homologue of tumor suppressor p53), a low expression of transferring receptor (CD71) and desmoglein 3 as well as LRIG1, the scaffold protein FERM lineated (basal layer of the epidermis, HF bulge, base of sebaceous gland, dermal papillae and dermis), that harbor different types of skin SCs 2:

a) Interfollicular epidermal SCs are scattered singly across the dermal-epidermal junction. In the mucosa and on the palms and soles, SCs are located at the base of the rete ridges. They constitute about 1%~7% of epidermal basal cells. Several human SC markers have been described, including high surface expression of α6 and β1 integrins that may be relevant for sustaining the attachment of epidermal SC to their basement membrane through hemidesmosomes. Progenies from epidermal SCs that withdraw from the cell cycle, show a suppression of integrin α6 expression, before they start differentiating and moving towards the skin surface, where they slough off along terminal differentiation after approximately 4 weeks33. Furthermore, p63 (a homologue of tumor suppressor p53), a low expression of transferring receptor (CD71) and desmoglein 3 as well as LRIG1, the scaffold protein FERM domain-containing protein 4A (FRMD4A), and CD46 have been established as interfollicular SC markers.

b) Beside tissue regeneration interfollicular SCs have been shown to be invested with the ability of generating hairs32. In HFs, several distinct SC-types have been identified. One multipotent SC population resides in the bulge located at the base of the HF (during telogene phase of hair development) or beneath the HF-associated sebaceous gland (in anagen phase). This follicular component is established during embryonic hair morphogenesis and resists periodic degeneration

during the hair growth cycle. Stimulation of these SC to exit their niche as well as their proliferation and differentiation to form mature HFs is closely linked to the hair growth cycle 3. HF bulge SC show expression of the molecular markers such as cluster of differentiation 200 (CD200), keratin 15 (K15), Lgr5+ and pleckstrin homology-like domain family A, member 1 (PHLDA1) as well as transcription factors Sox9+, Lhx2+ and NFATc126,36,37 Beside these epidermal SCs, another multipotent precursor cell population resides in HFs and dermal papillae that originate from the embryonic neural crest. These epidermal neural crest SCs (EPI-NCSCs) hold clonal multipotency that can give rise to melanocytic, neuronal and myogenic cell lineages in vitro and show differentiation potential toward mesenchymal lineages, as they are able to give rise to adipocyte, chondrocyte, and osteocyte progeny. Because of their advantageous physiological plasticity, multipotency, simple accessibility and non-controversial ethical issues, these EPI-NCSCs are considered promising donor cells for the repair of nervous system injuries 4.

Methodology: a) Sebaceous glands, attached to the HFs, are supposed to descend from different follicle SC populations, including Krt15+ bulge cells, LGR6+ and junctional zone SCs. Other studies describe the existence of periglandular Blump1-expressing sebaceous progenitors and a SC population within the gland itself 5. Progenitors give rise to terminally differentiated sebocytes that degenerate along holocrine secretion, releasing lipid-rich sebum into the hair canal that maintain an adequate lubrication of the skin surface 5.

b) Melanocyte SCs derive from the neural crest and permanently reside in the HF bulge, basal epidermis and probably also in the dermis 6. They give rise to pigment-producing melanocytes in the epidermis and the hair matrix. The fate of the melanocytes within the follicle is connected to the HF phases, where melanocytes proliferate and differentiate during anagen, and diminish through apoptosis in catagen 7. Dysfunction of this SC population results in pigmentation defects that phenotypically manifest as hair graying. The latter underlies an increased apoptosis of melanocyte SCs due to higher oxidative stress subsequent to the deficiency of anti-apoptotic Bcl2 protein that occurs with aging 8.

c) The steady remodeling of the dermis and fibroblasts as their primary cellular component is managed via mesenchymal SCs. They are located in the connective tissue within the dermis, surround HFs (especially in the follicular sheath and papillae) or are found among pericytes around blood vessels. Beside fibroblasts, dermal mesenchymal SCs generate myofibroblasts, endothelial cells, nerves, blood vessels, osteoblasts, chondrocytes and adipocytes 9. Morevoer, they are crucial for the coordination of the complex process of wound healing by attracting other host cells, growth factors and extracellular matrix (ECM) secretory proteins. Dermal SCs lack uniform distinctive markers but adhere to plastic in contrary to other SCs 10.

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STRESS AS AN OCCUPATIONAL HAZARD

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ABSTRACT

Changes in the body during stress are a combination of protective physiological reactions that arise in response to the effects of harmful environmental factors in the body for protection. Stress is the cause of many diseases; it harms human health, disturbs the well-being of people, and affects human activities. The daily professional activities of modern man are accompanied by an increase in mental and intellectual loads. The rhythm of modern tense life increases the possibility of developing professional stress and the number of "stressful" professions. One of such professions appears medical field. The study aimed to identify occupational stressors and identify health-related changes in medical professionals and develop recommendations for coping with occupational stress. The research has shown that the work environment of medical staff, particularly nurses, can be considered as a place where the employees are exposed to stressful factors; Stress factors can be considered as stressors:. dealing with overburdened and responsible work, the process of taking care of seriously ill patients, in particular, the need to make the right decision in a short time, as well as the need to carry out well-organized emergency medical interventions in a short time.
Keywords: occupational medicine, occupational stress, medical personal.

In the 21st century, the number of people experiencing stress effects has increased. According to the World Health Organization, 45% of all illnesses are related to stress. Besides, some experts believe that, in reality, the figures exceed the official data two times [6,11]. According to the analysis of the visits to the primary healthcare centers, 30-50% of the patients are practically healthy people who only need to improve their emotional state [11].

Changes in the body during stress are a combination of protective physiological reactions that arise in response to the effects of harmful environmental factors in the body for protection. Stress is the cause of many diseases; it harms human health, disturbs the well-being of people, and affects human activities. Studies show that up to 90% of all illnesses are "stress-dependent", e.i. related to stress. In recent years, professional stress problems have become increasingly common.

According to the American magazine "Psychology Today", 40% of Japanese teachers, one-fifth of British workers, 45% of US employees suffer from stress. The most common manifestations are depression and anxiety, with frequent headaches [11].

Stress factors in organizations have a significant impact on the quality of employee performance. Significant difficulties arise in accomplishing the set tasks and achieving the strategic goals of the organizations. In working teams, due to professional stress, the imbalance of group activities leads to a decrease in the effectiveness of the quality of work, increases personal dissatisfaction in each member of the team, and promotes staff turnover, etc. Occupational stress - this is a condition that is developed based on psychological tension and which leads to the depletion of human emotional and personal resources [12].

The daily professional activities of modern man are accompanied by an increase in mental and intellectual loads. The rhythm of modern tense life increases the possibility of developing professional stress and the number of "stressful" professions.

One of such professions appears medical field. 45% of medical staff and 67% of nurses suffer from stress-induced health disorders [9]. On the one hand, their professional activities are accompanied by physical and mental strain, which has a significant impact on the efficiency of work, and in some cases - significantly reduces its efficacy. It also causes the development of various diseases. On the other hand, patients also experience stress in a hospital setting. For a patient, a stress factor may be the environment, investigation results, manipulations, medical professionals' attitudes towards them, etc. The above-listed factors confirm the urgency of the stress problem and the need to ensure human resilience to stress in daily and extreme conditions.

Studies have shown that almost half of all the cases with incapacity to work in the communication professionals, particularly among medical workers, are related to stress. According to a survey, 41% of cases with high levels of anxiety and 26% cases with clinical depressions have been revealed among general practitioners in the UK. One-third of the physicians were taking medications to suppress emotional tension. The amount of alcohol consumed in the study group was above average [3,6].

Currently, specialists are paying more and more attention to new technologies for the prevention and coping with occupational stress [13, 3]. The research, over the last decade, has been focused on identifying the stressors of the work environment of medical professionals and developing measures to prevent the health disorders caused by them [1, 2,3,4,5,7,8,10].

The study aimed to identify occupational stressors and identify health-related changes in medical professionals and develop recommendations for coping with occupational stress.

The study has been conducted in several departments of the medical service institution, in particular in the Departments of Emergency Medicine, Resuscitation, Cardiology, and Multidisciplinary Departments. 131 nurses have been interviewed. Among them: in the Department of Emergency Medicine - 36 (23 women and 13 - men), in the Intensive Care Unit - 32 (women - 15, men - 17), in the Cardiology Department - 29 (all of them were females) and in the Multidisciplinary Department - 34 (women - 33, Men -1). The age of the respondents ranged from 20 to 58 years. Work experience - from 3 months to 39 years.

A special questionnaire has been developed - a questionnaire, which collected information about the age, sex, work experience, alleged stressors, and health status of respondents.

The information obtained from the survey of nurses working in each department was compared with each other. The main group was the staff of the Emergency Medicine, Resuscitation, and Cardiology Departments, and the control group was the Multidisciplinary medical staff.

The information obtained from the survey of the respondents was processed by statistical analysis.

The vast majority of respondents in both the main and control groups were females - 69% and 97%, respectively. Comparison of age groups showed that 55% of respondents were mostly 20-29 years old. The age of persons was approximately equal in the second age group and the main and control groups (30-39 years old). However, the control group had 7 times more employees over the age of 50 (21% of respondents) compared to the main group (3%).

It should also be noted that the seniority figures have been distributed as follows: the number of respondents has been almost equal in the control group with 6-9 and more than 10 years of work experience (41% and 45%, respectively) and 2.8 times more experience than the main group. A person with up to 1 year of work experience has not been found in any of the groups of the

respondents. However, the main group has had persons with 6 to 9 years of experience (61%) 1.5 times more than the control group (41%).
This age and seniority distribution, taking into account their professional experience, makes the respondents' answers about the assessment of work environment factors and their impact convincing.
A list of potential stressors was included in the questionnaire to clarify the environmental factors affecting the employees during the professional day job. The data obtained for this question are given in Diagram 1.

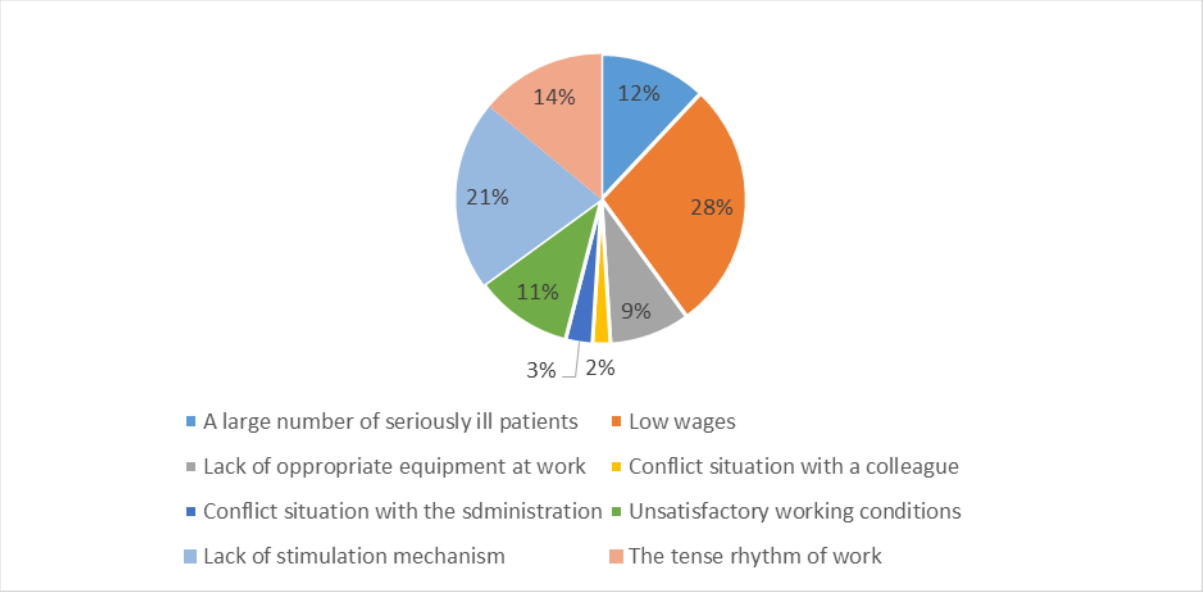

Diagram 1. Distribution of probable stressors in the main and control groups

The research has shown that the work environment of medical staff, particularly nurses, can be considered as a place where the employees are exposed to stressful factors; Stress factors can be considered as stressors:
A. dealing with overburdened and responsible work, the process of taking care of seriously ill patients, in particular, the need to make the right decision in a short time, as well as the need to carry out well-organized emergency medical interventions in a short time;
B. Low wages and unsatisfactory working conditions;
C. Lack of incentive mechanism and the possibility of developing a conflict situation during work performance;
The constant impact of stressors on the medical staff, leading to their health problems, among which pathological changes occur in the nervous and cardiovascular systems.

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СТРУКТУРА БРЫЖЕЕЧНЫХ ЛИМФАТИЧЕСКИХ УЗЛОВБЕЛЫХ КРЫСВ РАННЕМ ОНТОГЕНЕЗЕ

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Актуальность исследования: Лимфатическим узлам отводится важная роль в развитии иммунного ответа [1,2]. Кроме того, реакция лимфатических узлов в экстремальных условиях является одним из показателей адаптивных потенций организма к поддержанию тканевого гомеостаза [3]. Однако, мало изученными остаются вопросы об особенностях становления функциональных и структурных зон лимфатических узлов в раннем онтогенезе, что и послужило основой для настоящего исследования.

Цель исследования: Изучить динамику становления микроанатомической организации и клеточного состава брыжеечных лимфатических узлов в антенатальном и раннем постнатальном периодах развития у белых крысят.

Материал и методы исследования: Материалом для морфологического исследования явились40брыжеечные лимфатические узлы плодов и новорожденных белой крысы.
Экспериментальная группа состояла из четырех подгрупп животных. При этом были учтены закономерности развития беременности у белых крыс. Течение беременности у белых крыс состоит из четырех периодов [4]: I - 3-5 сутки беременности (доимплантационный период); II - 7-9 сутки (ранний постимплантационный период); III - 13-15 сутки (период функционирования зрелой плаценты); IV - 19-21 сутки (период старения плаценты). Распределение животных по условиям опыта представлено в таблице 1.
В работе были применены методы исследования, изложенные в классических руководствах по гистоморфологии [5, 6]: анатомические – препарирование, макроскопическое описание, взвешивание трахео-бронхиальных лимфатических узлов, фиксация; гистологические – окраска гематоксилином и эозином, азур 11 – эозином, по методу Фута; гистохимические – ШИК реакция; метод люминесцентно-микроскопического исследования [7]; морфометрические – определение морфологических параметров брыжеечных лимфатических узловс помощью окуляр – микрометра МОВ 1-15 и окулярной измерительной сетки Автандилова под микроскопом МБИ-3 с бинокулярной насадкой АУ-12; метод статистического анализа – статистическая обработка результатов проведена по программе «Медико – биологическая статистика» (2001).Статистическую достоверность различий оценивали по критерию Стьюдента.

Таблица 1 - Распределение экспериментального материала (крысята n = 40)

Эксперимен тальные животные	Возраст животных (в сутках)			
	Антенатальный период онтогенеза		Постнатальный период онтогенеза	
	13-16(I)	17-21 (II)	1-4 (III)	5-7 (IV)
Белые крысята (п-40)	10	10	10	10

Результаты исследования: Закладка брыжеечных лимфатических узлову потомства белых крыс выявлена на 15 сутки внутриутробного развития. Обнаружено становление лимфатических узлов, с момента закладки, до и после рождения животных. В связи с этим, на протяжении исследованного периода, нами выделены 4 этапа развития брыжеечныхлимфатических узлов, приходящиеся на 15-16 (I) и 17-21 (II) сутки антенатального и 1-4 (III) и 5-7 (IV) сутки постнатального периодов онтогенеза. Каждый этап развития характеризуется определенными преобразованиями их анатомических структур и клеточного состава.

У экспериментальных животныхI этапа развития (15-16 сутки) зачатки брыжеечных лимфатических узловимели на срезах треугольную и овальную формы, у 17-21 суточных плодов (II этапа) лимфатические узлы округлой и овальной формы, у новорожденных крысят (1-7 сутки жизни III-IV этапы) они становились бобовидными или подковообразными.

Морфологическое исследование брыжеечных лимфатических узлов показало, что площадь продольного срединного среза узлов (табл. 2) в течение исследованных периодов развития увеличивалась. Так, у плодов 15-16 сутки площадь продольного срединного среза брыжеечныхлимфатических узлов составила 1,08±0,004 мм^2, у плодов 17-21 сутки – 3,40±0,016 мм^2, у новорожденных крысят 1-4 сутки жизни –4,0±0,080 мм^{2}и 5-7 сутки жизни – 5,75±0,033 мм^2.

У плодовбелых крыс 15-16 сутки антенатального периода развитиябрыжеечные лимфатические узлы имели тонкую соединительно-тканную капсулу, состоящая из нежных коллагеновых волокон. Трабекулы не обнаружены. Краевой субкапсулярный синус выявлен, а промежуточные синусы не определены. К концу этого периода, т.е. у плодов 16 сутки внутриутробного развития уже появлялись промежутки между береговыми клетками выстилки подкапсулярного синуса. Дифференцировка паренхимы не наблюдалась. Выявлялись единичные тонкостенные кровеносные сосуды.

Таблица 2 – Результаты определения площади продольного сечения брыжеечных лимфатических узловв антенатальном и раннем постнатальном периодах развития у белых крысят (мм^2, M±m).

Лимфаузел	Период развития и возраст животных в сутки			
	Антенатальный		Постнатальный	
Брыжеечный	15-16	17-21	1-4	5-7
	1,08±0,004	3,40±0,016	4,0±0,080	5,75±0,033

У плодов I этапа развития удельная площадь (табл. 3) капсулы составила 0,92±0,01%, краевого синуса–18,52±0,49%, паренхимы – 80,56±1,90%.

Стереометрически (табл.4) у плодов белых крыс 15-16 сутки эмбрионального развития в брыжеечных лимфатических узлах выявлялись ретикулярные клетки и клетки лимфоидного ряда. Следует отметить, что на данном этапе развития доминирующим клеточным элементом являлись стромальные клетки и малые лимфоциты. Процентное содержание ретикулярных клеток составило 51,2±1,57%, малых лимфоцитов 20,0±1,22%. Кроме того, на данном этапе развития обнаружены средние и большие лимфоциты. Их количество составило 4,0±0,61% и 3,2±0,55% соответственно. В незначительном количестве обнаружены клетки с фигурами митоза до 0,8±0,28%. Содержание бластных форм клеток составило 5,6±0,72%. Плазмоциты и макрофаги не обнаружены.

У плодов белых крыс (II этап) 17-21 сутки антенатального периода развития соединительно-тканная капсула состояла из коллагеновых волокон. Толщина капсулы однородная. Трабекулы еще не определялись. Краевой синус обнаружен, однако, по сравнению с предыдущим сроком развития, его объем уменьшен. Несколько увеличена доля паренхимы. Из промежуточных синусов, выявлялись лишь мозговые синусы(табл. 3).

Удельная площадь капсулы(табл. 3), в сравнении с 1-ым этапом развития, увеличена и составила– 1,18±0,03%. Отмечено уменьшение удельной площади краевого синуса по сравнению с предшествующим сроком. Так, объем краевого синуса составил– 5,59±0,43%, что в 3,5 раза меньше, чем в предшествующей группе. Доля паренхимы в этом сроке развития (II этапа) несколько увеличена. Её удельная площадь составила – 92,06±1,13%т.е. приблизительно на 12% больше, чем в I-ом этапе развития. Мозговой синус в брыжеечныхлимфатических узлахобнаружен и его площадь составила1,17±0,46%.

Лимфоидная ткань продолжала сохранять свою диффузность. Клеточные элементы на площади среза брыжеечных лимфатических узлов распределены равномерно.

Клеточный состав брыжеечных лимфатических узлову плодов белых крыс 17-21 сутки антенатального периода развитияпретерпевал определенные изменения по сравнению с предыдущим сроком. Цитограммы паренхимы показали, что происходит рост числа всех клеток лимфоидного ряда (табл. 4). Процентное содержание малых лимфоцитов достигало– 33,6±1,49%, средних лимфоцитов –10,8±0,99%, больших лимфоцитов –7,2±0,82%. Наблюдалось увеличение количества клеток с митозом в 2 раза, в сравнении с предшествующей группой. Отмечен рост количества бластных форм клеток до 8,0±0,87%.На фоне увеличения клеток лимфоидного ряда, доля стромальных клеток снижена до 35,2±1,50%, в предыдущем сроке развития – 51,2±1,57%, что на 16% меньше. Плазмоциты и макрофаги не обнаружены.

У новорожденных крысят 1-4 сутки жизнив раннем постнатальном периоде развития происходили значительные преобразования в структурных компонентах и клеточном составе брыжеечных лимфатических узлов.Наблюдалось увеличение удельной площади капсулы (табл.3)– 1,25±0,08%. Толщина капсулы равномерная. Трабекулы, по-прежнему, не определялись. Объем краевого синуса уменьшен по сравнению с предшествующей группой. Так удельная площадь подкапсулярного синуса составила 4,25±0,41%. Объем мозговых синусов в брыжеечных лимфатических узлах составил 1,50±0,31%.

Паренхима продолжала по-прежнему сохранять свою диффузность. Удельная площадь ее составила составила86,25±1,01%, т.е. отмечено снижение объема паренхимы по сравнению с

предыдущим сроком. Это явление связано с появлением промежуточных синусов. Так, объем мозговых синусов в брыжеечных лимфатических узлах составил 1,50±0,31%.

На данном этапе развития изменялось и распределение различных видов клеток в составе клеточной популяции (табл.4). Значимо увеличивалось процентное содержание малых лимфоцитов с 33,6±1,49% до 52,0±1,57%, т.е. на 18,4%. Доля средних лимфоцитов возрастала до 12,8±1,04% т.е. на 2%. Клетки с фигурами митоза, так же, как и в предыдущем сроке, имели тенденцию к увеличению. У новорожденных крысят 1-4 сутки их количество в брыжеечных лимфатических узлах увеличено в 2 раза по сравнению с предшествующей группой (табл. Б.9). Что касается содержание бластов и больших лимфоцитов, то их доля, в отличие от предыдущих сроков развития, у новорожденных крысят снижена. Так, число больших лимфоцитов уменьшено2,3 раза; бластных форм клеток– 2,5 разапо сравнению с предшествующей группой.

Плазмоциты по прежнему не выявлялись. Появлялись единичные дегенерирующие клетки. В отличие от предыдущего срока, у новорожденных крысят обнаруживались макрофаги, их число составило вбрыжеечных лимфатических узлах 3,2±0,55%.

Таким образом, к концу III этапа развития, в паренхиме брыжеечных лимфатических узловначинают преобладать малые лимфоциты (табл. 4).

В течение 1-4 сутки постнатального периода развития в брыжеечных лимфатических узлах значимо снижались показатели стромальных клеток. Количество ретикулярных клеток в конце срока составило 17,6±1,20%, т.е. на 17,6% меньше, чем в группе предыдущего срока развития(табл. 4).

У новорожденных крысят 5-7 сутки жизни в раннем постнатальном периоде развития продолжалось развитие брыжеечных лимфатических узлов. Увеличивалась удельная площадь капсулы до 1,2±0,02%. Объем краевого синуса, также как и в предыдущих сроках, имел тенденцию к снижению. Так, площадь краевого синуса уменьшена до 2,67±0,18% т.е. в 1,6 раза по сравнению с предыдущим периодом (табл. 3).

В отличие от предыдущих сроков развития, у крысят однонедельного возраста появлялась паракортикальная зона. Ее площадь составила 3,83±0,21%. Происходила дифференцировка паренхимы на корковое и мозговое вещества, что не наблюдалось во всех сроках предыдущего периода развития (рис).

Объем коркового вещества сохранился на прежнем уровне по сравнению с предыдущим периодом. Площадь мозгового синуса имела тенденцию к увеличению. Его удельная площадь составила 1,74±0,73%. Доля мозговых тяжей составила 6,96±0,56%, (табл. 3).

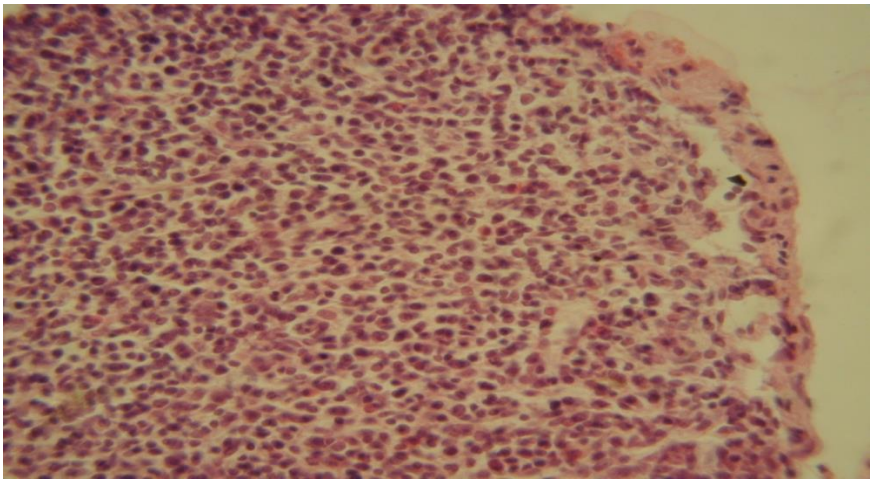
В связи с дифференцировкой паренхимы на корковое и мозговое вещества, клеточный состав лимфатических узлову новорожденных крысят 5-7 сутки жизни в раннемонтогенезе претерпевает значительные изменения в сравнении с предыдущим сроком(табл. 4).

В корковом веществебрыжеечных лимфатических узлов основными клеточными элементами являлись малые лимфоциты, среднее количество которых составило 60,0±1,52%. На долю средних лимфоцитов приходилась 14,4±1,17%. Это больше по процентному содержанию, чем в предыдущем сроке. Число больших лимфоцитов было меньше в 4 раза, чем в предшествующей группе.На прежнем уровне сохранялось количество клеток с митозом. Отмечено снижение содержания бластных форм клеток. Их число снижено до 2,4±0,48%.

Плазмоциты, макрофаги и дегенерирующие клетки в корковом веществе брыжеечсных лимфатических узлов у однонедельных крысятне обнаружены. Процентное содержание

стромальных клеток составило 16,0±1,15%, что ниже, чем в предыдущем сроке развития (табл. 4).

Так же, как и в корковом веществе, преобладающим видом клеток в мозговом веществе брыжеечных лимфатических узлов однонедельных животных оставались малые лимфоциты. Однако, их количество было меньше, чем в корковом веществе. Так, процентное содержание малых лимфоцитов составило 32,0±1,47%. Средние лимфоциты занимали второе место в клеточной популяции лимфоидного ряда мозгового вещества. Их доля здесь в брыжеечных лимфатических узлах –



Дифференцирование паренхимы на корковое и мозговое вещество. Формирование паракортикальной зоны. Окраска гематоксилином и эозином. Об. 20, ок. 10.
Рисунок - Брыжеечный лимфатический узел новорожденной крысы на 7 сутки жизни в условиях физиологического развития.

Таблица 3 – Результаты определения (%) сечениястуктур брыжеечных лимфатических узлов (БЛУ) у потомства белых крыс в раннем онтогенезе (M±m)

Структурные компоненты лимфатического узла	Лимфат ичес-кий узел	Период развития и возраст животных в сутки			
		Антенатальный		Постнатальный	
		15-16	17-21	1-4	5-7
Капсула	БЛУ	0,92±0,01	1,18±0,03	1,25±0,08	1,2±0,02
Краевой синус	БЛУ	18,52±0,49	5,59±0,43	4,25±0,41	2,67±0,18
Корковое плато	БЛУ	80,56±1,90	92,06±1,13	86,25±1,01	82,96±0,09
Лимфатический узелок	БЛУ	-	-	-	-
Паракортикаль-ная зона	БЛУ	-	-	-	3,83±0,21
Мозговые тяжи	БЛУ	-	-	-	6,96±0,56
Мозговой синус	БЛУ	-	1,17±0,465	1,50±0,31	1,74±0,73
Примечание: БЛУ – брыжеечный лимфатический узел;					

Их доля здесь в брыжеечных лимфатических узлах –18,4±1,23%. В мозговом веществе брыжеечных лимфатических узлов довольно большое количество больших лимфоцитов – 4,0±0,61%, что больше, чем в корковом веществе (табл. 4).В отличие от коркового вещества, в мозговом обнаруживались плазмоциты и макрофаги. Их процентное содержание составило 4,8±0,67% и 4,9±0,73%соответственно. Отмечено снижение доли ретикулярных клеток. Их количество составило 13,6±1,03%. В мозговом веществе имелись единичные клетки с митозом (табл. 4).

Таблица 4 – Содержание клеток (%) в брыжеечных лимфатических узлах у потомства белых крыс в раннем онтогенезе (M±m):

Клетки	Лимфа узел	Период развития и возраст животных в сутки				
		Антенатальный		Постнатальный		
		15-16	17-21	1-4	5-7	
		Паренхима зачатка узла	Паренхима узла	Паренхима узла	Корковое вещество	Мозговое вещество
Бласты	БЛУ	5,6±0,72	8,0±0,87	3,2±0,55	2,4±0,48	2,4±0,46
Митозы	БЛУ	0,8±0,28	1,6±0,39	3,2±0,55	3,2±0,55	0,8±0,28
Большие лимфоциты	БЛУ	3,2±0,55	7,2±0,82	3,2±0,55	0,8±0,28	4,0±0,61
Средние лимфоциты	БЛУ	4,0±0,61	10,8±0,99	12,8±1,04	14,4±1,17	18,4±1,23
Малые лимфоциты	БЛУ	20,2±1,22	33,6±1,49	52,0±1,57	60,0±1,52	32,0±1,47
Плазмоциты	БЛУ	-	-	-	-	4,8±0,67
Макрофаги	БЛУ	-	-	3,2±0,55	-	4,9±0,73
Дегенериру ющие клетки	БЛУ	-	-	0,8±0,28	-	1,6±0,39
Ретикулярны е клетки	БЛУ	51,2±1,57	35,2±1,50	17,6±1,20	16,0±1,15	13,6±1,03
Примечание: БЛУ – брыжеечный лимфатический узел;						

Таким образом, у новорожденных крысят 5-7 сутки жизни в раннем постнатальном периоде развития происходят значительные преобразования в микроанатомической организации и клеточном составебрыжеечных лимфатических узлов, как периферический орган иммуногенеза. Однако, лимфоидные узелки еще не формируются.

Выводы: 1. На протяжении исследованных этапов развития брыжеечных лимфатических узлов, по степени дифференцировки паренхимы и стромы можно выделить четыре этапа, которые соответствуют следующим срокам: I-этап – 15-16 сутки антенатального развития; II-этап – 17-21 сутки антенатального периода; III-этап – 1-4 сутки постнатального развития; IV-этап 5-7 сутки постнатального периода.
2. На 5-7 сутки постнатального развития у потомства белых крыс брыжеечные лимфатические узлыприобретают черты сформированногопериферического органа иммуногенеза, выполняющего свои иммунологической, лимфопоэтической и барьерной

функции, о чем свидетельствуют полученные иммуноморфологические данные: дифференцировка паренхимы на Т-зоны (паракортикальная область) и В-зоны (мозговое вещество); формируются краевые и промежуточные мозговые синусы.

3.Проведенные исследования позволяют лучше понять закономерности строения и развития органов иммуногенеза, позволяя стандартизировать иммуноморфологические данные в процессе физиологического онтогенеза.

Таблица Б.8 – Содержание клеток (%) в брыжеечных лимфатических узлах у потомства белых крыс в раннем онтогенезе (M±m)

4.Полученные данные о иммуноморфологиибрыжеечныхлимфатических узлов могут быть использованы морфологами и иммунологами, как эталон, для оценки состояния периферических органов иммуногенеза при экспериментальных исследованиях.

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КЛИНИЧЕСКИЙ СЛУЧАЙ: ВТОРИЧНАЯ В-ЗРЕЛОКЛЕТОЧНАЯ ЛИМФОМА У РЕБЕНКА ПОСЛЕ ЗАВЕРШЕНИЯ ПРОТИВООПУХОЛЕВОЙ ТЕРАПИИ ПО ПОВОДУ ОСТРОГО МИЕЛОБЛАСТНОГО ЛЕЙКОЗА.

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Актуальность: В лечении онкологических больных в последние годы достигнуты существенные успехи. Изменения привели к улучшению показателей выживаемости и более длительной продолжительности жизни. В связи с этим все большую актуальность приобретает изучение риска развития вторых первичных опухолей. Больные, получившие лечение по поводу первого злокачественного новообразования, остаются в группе повышенного риска развития второй опухоли на протяжении всей последующей жизни. Риск развития вторых и последующих опухолей у пациентов с уже выявленными опухолями примерно в 1,3 раза выше, чем у лиц, у которых ранее не было новообразований.
Ключевые слова: ОМЛ, вторые опухоли у детей, В-лимфома, опухоли, противоопухолевая терапия.

Цель: ознакомить педиатров, ВОП врачей, детских онкологов-гематологов со случаем развития второй первичной опухоли у ребенка, ранее перенесшего злокачественное новообразование.

Основная информация: Ежегодно в последние годы регистрируется около 70–80 детей и 20 подростков с диагнозом злокачественного новообразования.
У детей ОМЛ составляет около 20% острых лейкозов. Ежегодно заболевают 0,5- 0,7% на 100.000 детского населения (12-15 детей) в год и имеют худший прогноз (71% - долгосрочно выживших). В абсолютном большинстве случаев ОМЛ является спорадическим заболеванием, причиной которого являются многоэтапные кооперирующие мутации (точечные, аномалии числа копий, транслокации) в гемопоэтических клетках-предшественниках, результатом которых является прекращение линейной гематологической дифференцировки и неконтролируемая пролиферация злокачественных аналогов миелоидных предшественников.

Частота: У детей в структуре злокачественных опухолей первое место занимает лейкозы (32-34,0%), второе — опухоли ЦНС (14-17,0%), третье – ЛХ и НХЛ (11-14,0%), а четвертое — солидные опухоли (нефробластома, нейробластома, остеогенные саркомы, опухоли мягких тканей и др.)
Заболеваемость: В настоящее время показатели заболеваемости детей в возрасте от 0 до 15 лет колеблется 15-20% в год. Так, в Германии этот показатель в 1992 г. — 14,6%, и подобная тенденция просматривается, как в европейских странах, так и в США [5].

Стабильная заболеваемость детей лейкозами — около 4,0% детей в год, зарегистрированная в течении последних 15-20 лет, позволяет экстраполировать эти данные на следующее десятилетие. Аналогичные процессы регистрируются и в Казахстане, где за последние 8-10 лет показатель заболеваемости детей лейкозами составил от 2,8% до 3,2% в год. [4].
Исследователи из Великобритании проанализировали выживаемость, частоту рецидивов и отдаленные исходы у 272 пациентов, успешно пролеченных в возрасте до 21 года от ОМЛ. Выживаемость составила 97% в течение 10 лет наблюдения и 94% — в течение 20 лет. Зарегистрированы 10 вторых опухолей у восьми пациентов, четыре из которых получали ЛТ [6].
Наибольший риск возникновения новообразований характерен для детей в возрасте 0–4 года. Наибольший показатель онкологической заболеваемости выявлен для мальчиков в возрасте 1–4 года, наименьший у девочек 10–14 лет.
Пациенты с ОМЛ в 25–30 % в возрасте от 0 до 18 лет могут столкнуться с рецидивом лейкоза, 5–10 % гибнут от осложнений заболевания и/или побочных эффектов терапии и.т.д. [4]

Злокачественные лимфомы это рак, который появляется в клетках лимфатической системы. Основной симптом - увеличенные лимфатические узлы. Злокачественные опухоли лимфатических узлов встречаются у 12% детей и подростков, заболевших раком. Среди онкологических заболеваний - это третья по распространённости болезнь. В Германии ежегодно регистрируют около 210 новых пациентов. Лимфомы делят на два основных типа: лимфома Ходжкина (болезнь Ходжкина) и большая группа неходжкинских лимфом. Лимфомы, как и острые лейкозы, поражают весь организм человека, поэтому называются системной злокачественной болезнью.
Зарубежные и российские данные свидетельствуют о том, что современные возможности лечения опухолей детского возраста улучшили прогноз, но одновременно увеличили риск развития вторичных опухолей (ВО). В среднем вероятность развития ВО составляет 2 - 5 % за последние 20 лет. Имеются некоторые факторы риска, связанные с проведенной терапией при лейкозах, таких как применение Лучевой терапии, более ранний возраст на момент диагноза первого ЗН, наследственная предрасположенность, женский пол, и получение высоких доз алкилирующих препаратов (циклофосфамид, ифосфамид, цисплатин, карбоплатин, мелфалан), ингибиторов топоизомеразы II (этопозид) и антрациклинов (доксорубицин или даунорубицин) увеличивают риск развития ВО в 5 раз и сокращают латентный период. [3] Риск нарастает с длительностью прослеживания. Наиболее частые опухоли: опухоли костей, МДС, ОМЛ [2,3].
Опухоли, которые наиболее часто сопровождаются ВО — это лимфома, ретинбластома, медуллобластома, нейробластома и лейкозы.
В Республике Белорусь проведен анализ за период с 1989 по 2007 гг. 59 пациентов в возрасте от 1,5 года до 35 лет, получавших лечение по поводу ЗН в детском и подростковом возрасте, выявлена вторая злокачественная опухоль. Метахронные вторые ЗН (свыше 6 мес после установки ПО) диагностированы в этот временной период в возрасте от 1,5 года до 17,5 года у 54 пациентов[1].
По данным НИИ детской онкологии и гематологии РОНЦ им. Н.Н. Блохина с 1977 по 2008 г. включительно получили лечение 13392 первичных ЗНО. Пятилетняя выживаемость составила 56,5 % (6 950 детей). Были проанализированы данные 86 пациентов (1 ,2 %) у

которых в различные сроки окончания противоопухолевой терапии (от 9 до 216 мес, в среднем через 8,5 лет) по поводу ПО диагностировано возникновение второй опухоли. Наибольшее количество на долю ПО приходится на ОЛЛ (5, 1 ,2 %), ЛХ (3 3 ,3 %), НХЛ (15,3 %) и **только 1 случай ОМЛ**. [1]

В группе больных со вторыми опухолями среди первых ЗН преобладали солидные опухоли, составляя 52 %, гемобластозы – 48 %.

Лимфомы (заболеваемость один ребенок из 4000 в возрасте до 15 лет) встречаются в основном у подростков и взрослых, в то время как у маленьких детей они встречаются редко. Лимфомы Ходжкина встречаются примерно на 50% чаще у мальчиков. Пациенты с лимфомой Ходжкина показали хороший прогноз на протяжении десятилетней терапии (текущая долгосрочная выживаемость составляет 97%) [5]

В течение 30 лет (с 1981г. по 2013г.) в Германии вторичные лимфомы имели место в 21 случаях (1,7% от всех зарегистрированных 1245 случаев). [5]

Учитывая вышеизложенные данные, хотелось бы обратить особое внимание на образование вторичных опухолей после окончания лечения первичного злокачественного заболевания.

Представленный ниже клинический случай описывает образование вторичной опухоли в виде лимфомы, после окончания курса по первичному ОМЛ.

Материалы: Пациент А, 5 лет с диагнозом - Острый Миелобластный Лейкоз, М4-М5 вариант, коэкспрессия лимфоидного антигена CD4 (от 11.04.2018г.) и В-зрелоклеточная лимфома с поражением л/узлов, (шейных, над- и подключичной области слева, бронхопульмональных, внутрибрюшных, параковальных, парааортальных, печени, единично селезенки и почек с 2-х сторон (от 03.04.2019г.).

Из анамнеза жизни: Ребенок от 3 беременности, от 3 физиологических родов. Обращает внимание, что ребенок не прививался по религиозным соображениям, часто болел ОРВИ, бронхитом.

Из анамнеза заболевания: Ребенок впервые заболел остро в апреле 2018г. (в возрасте 2-х лет) на основании лабораторных данных (**бластоз 88%,** анемия 3 ст, Hb- 30г/л, гиперлейкоцитоз- 95,5 *10^9/л, тромбоцитопения 23 тыс.)

Миелограмма от 13.04.2018г. представлена на 69,6% бластными клетками. Ядра полиморфные с дисперсной структурой ядерного хроматина, имеется азурофильная зернистость и палочки Ауэра. Цитохимия: реакция на Миелопероксидазу в бластах 100% положительная. Липиды -100% положительная. **Заключение: ОМЛ. (**рисунок 1**)**

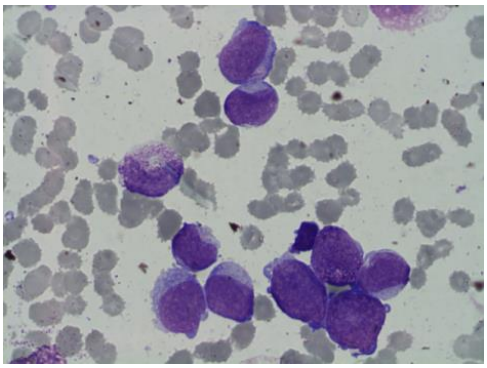

Рисунок 1. Миелограмма

ИФТ от 10.04.2018г. Суммарный фенотип патологической популяции CD14+CD117+CD33+CD15+CD11c-HLA-DR+CD34-MPO+ более всего соответствует **M4-M5 вариантам ОМЛ (В2). Коэкспрессия лимфоидного антигена CD4.**
На основании лабораторных данных, миелограммы, ИФТ выставлен диагноз: от 13.04.2018г. был установлен диагноз: ОМЛ, М4-М5 вариант, коэкспрессия лимфоидного антигена CD4. С апреля 2018г по сентябрь 2018г. проведен курс ИПХТ по протоколу AML-BFM 2004 (в полном объеме).
В контрольной миелограмме верифицирована ремиссия ОМЛ.
На 5 месяце поддерживающей химиотерапии (ПТ начата с 24.09.2018 г. наблюдалось ухудшение состояния в виде гипертермического синдрома, явлении фолликулярной ангины (февраль 2019г.).
Находился на стационарном лечении в АРДКБ с 05.02.19г- 25.02.19г, далее был переведен в НЦПиДХ для дальнейшего дообследования и возможного специализированного лечения.
В ОАК от 25.02.19г анемия 2 ст. (Нв-76 г/л), лейкопения (2,46 тыс), моноцитоз (23%), ускоренное СОЭ (60 мм/час). Учитывая стойкий гипертермический синдром и налет на ротоглотке с целью исключения рецидива сделана костно-мозговая и люмбальная пункция..
Ликвограмма и миелограмма от 27.02.2019г. и повторная миелограмма от 20.03.2019г. - без патологических изменений.
FISH исследование костного мозга от 10.04.2019г – перестроек не выявлено.
По лабораторным данным ремиссия по острому миелобластному лейкозу сохраняется.
У ребенка удерживалась стойкая гипертермия, налет на ротоглотке и в динамике отмечалось увеличение шейных лимфоузлов, в связи с этим проведена операция и гистологическое исследование шейного лимфоузла (март 2019г.).

Заключение от 20.03.2019г.: Морфологическая картина и иммунофенотип соответствуют диффузной крупноклеточной В-клеточной лимфоме, анапластический вариант.
На КТ ГМ + лицевого черепа от 26.03.2019г. КТ картина внутренней гидроцефалии, субкомпенсированная форма. Перивентрикулярная лейкомаляция. КТ картина пансинусита, 2-х стороннего отита. Выраженная лимфаденопатия шейных л/у с обеих сторон. Увеличение трубных и небных миндалин.
На КТ ОГК+ОБП+ОМТ с к/у от 04.04.2019г. Заключение: Образование над-подключичной области слева с переходом в передне- заднее средостение. Увеличение

бронхопульмональных л/у. Инфильтрат S6 слева. Лимфаденопатия внутрибрюшных л/у, паракавальных и парааортальных. МТС поражение, печени, единично селезенки и почек с 2-х сторон. Гепатоспленомегалия. Пневмония очагов-сливная средней доли справа, осложненная ателектазом.

На основании клинических данных, заключения КТ и иммуногистохимии выставлен диагноз: В-зрелоклеточная лимфома с поражением л/узлов и с апреля 2019г. начато лечение по протоколу B-NHL BFM 04. На этапе лечения, после завершения циторедуктивной профазы у ребенка купировался гипертермический синдром и в продолжении курса лечения получил блоки АА №1, ВВ № 1, СС № 1, АА №2. После 4-го блока АА№2, родители с ребенком уехали в Турцию, где от 04.11.2019г. ребенку была проведена –Аллогенная трансплантация гемопоэтических стволовых клеток, от родного брата (10/10). Состояние ребенка после АллоТГСК удовлетворительное, ребенок находится на динамическом наблюдении в дневного стационара НЦПиДХ.

Заключение: У ребенка с ОМЛ, получившего полный курс лечения по протоколу AML-BFM 2004 через год диагностирована вторичная опухоль В-зрелоклеточная лимфома с поражением лимфоузлов. В связи с чем ребенок получив 4 блока по протоколу B-NHL BFM 2004 (блоки АА, ВВ, СС, АА №2) затем проведена АллоТГСК. Состояние ребенка улучшилось, наступила клинико-гематологическая ремиссия, но продолжено динамическое наблюдения.

Вывод: Изучение вторых первичных опухолей у детей, получивших противоопухолевую терапию, представляет особый интерес, так как экспозиция детей к вредным факторам окружающей среды и образу жизни меньше, чем у взрослых. По литературным данным появление ВО связывают со снижением иммунитета после специфического противоопухолевого лечения и канцерогенным воздействием противоопухолевого, химио- и лучевого лечения и генетическими нарушениями. Дети с ЗН получают интенсивную лучевую и химиотерапию в период, когда их органы находятся еще на стадии развития, т.е. когда дети еще наиболее уязвимы. Следует помнить, что пролеченный в детстве по поводу злокачественной опухоли больной должен находиться в "группе риска" по вторичной опухоли и находится под динамическим наблюдением онколога, а так же проведение в декретированные сроки комплексного обследования с учетом тех органов и систем, в которых развитие вторичных опухолей наиболее вероятно.

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CLINICAL CASE: SECONDARY MATURE B- CELL LYMPHOMA IN A CHILD AFTER COMPLETION OF ANTITUMOR THERAPY FOR ACUTE MYELOBLASTIC LEIKEMIA

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Relevance: Significant advances in the treatment of cancer patients have been made in recent years. The changes have led to improved survival rates and longer life expectancy. Therefore, the study of the risk of developing second primary tumors is becoming increasingly important. Patients who received treatment for the first malignant neoplasm remain in the group with an increased risk of developing a second tumor throughout their subsequent life. The risk of developing second and subsequent tumors in patients with already identified tumors is approximately 1.3 times higher than in those who did not have any early tumors.
Keywords: AML, secondary tumor in children, B-lymphoma, tumor, antitumor therapy.

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A PERSISTANT BULLOUS PEMPHIGOID CASE STARTING AFTER COUMADIN USE

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ABSTRACT

Bullous pemphigoid is an autoimmune blistering disease characterised by subepidermal bullous eruption. Its majör property is having autoimmune antibodies targeted to hemidesmosomes BP230 and BP180[1]. A 64 year-old woman came to our clinic having painful bullous leisons widespread on trunk and all extremities. There were also painful erosions in oral mucousa. Most of her bullous lesions were eroded. She gave a history of many drug use because of her chronic diseases. These were multi antibiotics, antidiabetics, NSAIDs,and oral coumadin treatment.

Keywords: bullous pemphigoid, coumadin, blistering disease

Introduction: Bullous pemphigoid is an otoimmune blistering disease characterised by subepidermal blisters. Its majör property is having autoimmune antibodies targeted to hemidesmosomes BP230 and BP180 [1].

Case: A 64 year-old woman came to our clinic having painful bullous leisons in oral mucousa,on trunk and all extremities for a few months (Figure 1,2,3).

FIGURES

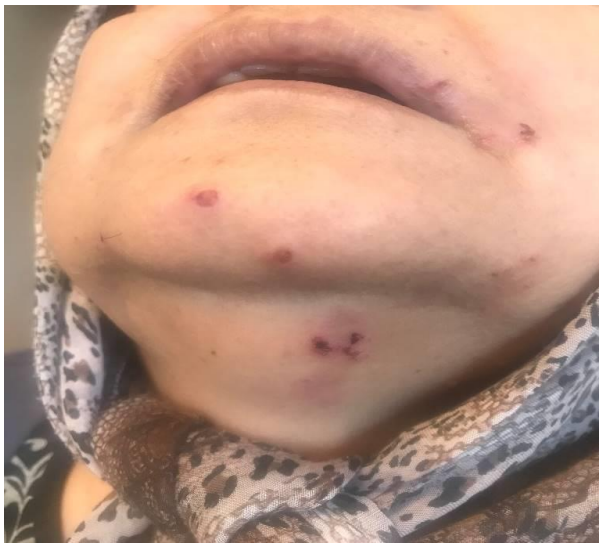

Figure 1 bullous leisons on face

Figure 2 bullous leisons on lower extremities

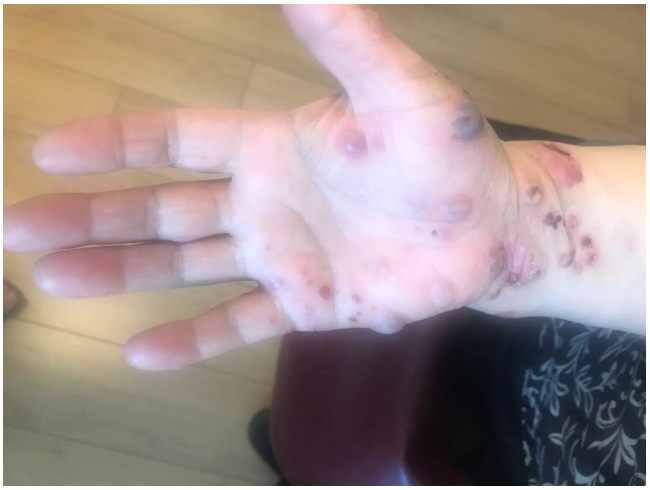

Figure 3 bullous leisons on hand

Most of the bullous lesions were large, tense and were turning to eroded and crusted wounds after a few weeks of survival. She gave a history of a persistan erytema, intractable pruritus and urticarial lesions for two months before the onset of bullous lesions. She was prescribed topical steroids and oral antihistaminic drugs before. As she told this treatment didn't work and the lesios changed and many painful blisters developed in months. She had frequently repetative urinary system infections due to persistant urethral stricture formed after as a complication of total hysterectomy operation. She had to use many antibiotics, antidiabetics, cardiac drugs for her comorbidities. In her last hospitalization she had to use coumadin for the first time. She definitely says the pruritic eczematous lesions started a few weeks after the start of this drug. Her urologist stopped the drug after lesions, but lesions didn't regress. After the exacerbation of the pruritus and blistering lesions patient came to dermatology outpatient clinic. She was given topical potent steroid ointments. She gave a history of using about one month of topical ointment alone, but didn't work. When she came to our clinic a skin biopsy and a sample for direct immune flourescent staining was taken. Topical potent corticosteroid, oral doxicycline (100 mg/day) and nicotinamide (1000 mg/day) was started as a first line systemic treatment. In laboratory results WBC: 9100, Sedimantation: 20, BUN:35.5 creatinine :1,25 AST: 12.7 ALT: 11.5 Total IgE: 5.41 and IgA: was 88.1. Her lesions didn't regress after 2 weeks. She was started oral prednisolone treatment of 48 mg and azathioprine after consulting to nephrology. Lesions started to regress. In this duration the patient had to be hospitalized because of ileus by general surgery and couldn't take the systemic dermatologic treatment for a few weeks. Her lesions were exacerbated widely. Her skin biopsy was resulted and reported as bullous pemphigoid. Since she had osteoporosis, diabetics and not well cured by first-line and second -line bullous pemphigoid medications she was started to be treated by intravenous immune globülin (IVIG) treatment and her systemic steroid dosed decreased to lower the risk of comobidities but wasn't totally leaved. Her lesions started to regress in a few months. But flare up was observed as the treatrment of IVIG was postponed a few days or weeks. She is under this medication for about 1,5 years.

Discussion: Bullous pemhigoid is a common seen autoimmune blistering disease in eldery. Its etiology is not totally found out. Most of the cases were reported to have relations with the medications. The medications related to disease were[2,3] Antirheumatics amphiciline[4] , antiaritmik drugs, antihypertensives (Ca canal blockers, amlodipine, nifedipine), ACE inhibitors (kaptopril, enalapril, lisinopril), beta blockers (nadolol, proctolol) ,Angiotensin II antagonists (losortan),vaccines (influensa, Swine flu, Tetanous toxoid, HZV; Hexavalented combined vaccines, NSAIDs[5] (azopropan, diclophenactopical, ibuprofen, mefanamik acid, fenasetins,Saliciylates (aspirin, sulphasalazin, Salisalazosulphapyrid), diuretics (furosemid, spironolactone), antidiabetics (sitagliptin, tolbutamide, vildagliptin Anti TNF-a drugs(Adalimumab Efalizumab, Etanersept) Antirheumatics (D-penicillamin,tiobutarit) arsenic ,clonidine ,erlotinib, fluoxetine, flupenthixol, gabapentine[6] ,galantamine hydrobromide, gold thiosulphate, Interleukin-2, levetiracetam, methyldopa, terbinafine thiopronin,omeprazole, psoralen placental extracts, potasyum iodid, risperidon, sulphonamid[7].

Conclusion: In our case as our patient was using many drugs as urologic systemic drugs, antibiotics, antidiabetics and for other chronic diseases. But she definetely gave a history of onset of pruritus and urticarial lesions starting after approximately two weeks of using oral coumadin. Oral coumadin treatment can be one of the drugs triggering bullous pemphigoid.

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POST COVID-19 NEUROLOGICAL SYNDROME (PCNS) IN AN 11 YEARS OLD BOY, A CASE REPORT

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ABSTRACT

By now more than 92.6[1] persons have been reported to be infected with COVID-19, of which significant part are children. Although children experience milder symptoms compared with adults at the time of the infection, cases of post-covid-19 complications have been reported (2, 3, 4, and 5). Complications might also include the CNS, in our case with cerebellar ataxia-like and polyneuritis-like signs and symptoms.
A 13 year old boy was presented in our clinic with signs of ataxia, occasional vomiting, impaired gait, impaired patellar reflexes on the right leg, incomplete Babinski reflex on the right leg, paresis of the left facial nerve and mild hypertension. Based on the clinical appearance and the parameters that showed past COVID-19 infection, a diagnosis of Post-COVID19 Cerebellar Ataxia-like and Polyneuritis-like was made, meaning a Post Covid-19 Neurological Syndrome (PCNS). Treatment was conducted with antibiotics and immunoglobulins resulting in significant improvement in the following days.
There are few reported cases about neurological complications caused by COVID-19 in children and adolescents, without any other symptoms of the virus. This is one of the first cases of Post-COVID19 Cerebellar Ataxia and Polyneuritis in a child as a result of COVID-19 and the first case in our country.
Keywords: Post-COVID19 complications, Post Covid-19 Neurological Syndrome, cerebellar ataxia, polyneuropathy, children

Introduction; As inflammation is a common reaction to biological insult, many conditions may present with features of neuritis. Common causes include autoimmune diseases, infection, either bacterial or viral, post-infectious immune reaction or a response to physical injury (6, 7).
Coronavirus disease-19 (COVID-19) is firstly a respiratory disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). Its pathobiology begins with targeting the angiotensin enzyme two (ACE-2) receptors which are present throughout the body, including neural tissues leading to endothelial dysfunction also at the neuro-vascular units in the brain. On-going hyperinflammation and endotheliitis contribute to the disruption of the blood-brain barrier, allowing entry of innate immune cells into the brain and further pro-inflammatory cytokine cascades (16). COVID-19 seems to be able to promote a hypercoagulable state through unique mechanisms and cross-talks between thrombosis and inflammation (17,18). Recent publications highlight the emerging evidence of a new syndrome- Post Covid-19 Neurological Syndrome (PCNS) with Chang and

colleagues describing patients with prolonged muscle weakness and other forms of myopathy among SARS-CoV survivors in Hongkong [19].

Cerebellar ataxia is a form of ataxia originating in the cerebellum[8], that can occur as a result of many diseases and may present with symptoms of an inability to coordinate balance, gait, extremity and eye movements.[9] Lesions to the cerebellum can cause dyssynergia, dysmetria, dysdiadochokinesia, dysarthria and ataxia of stance and gait.[10]

Polyneuropathy is damage or disease affecting peripheral nerves (peripheral neuropathy) in roughly the same areas on both sides of the body, featuring weakness, numbness, and burning pain.[11]

These two entities may develop as a post-infectious consequence that often presents itself several weeks after the resolution of the acute infection. In our case report they are both result from an asymptomatic COVID-19 infection.

Case Report: We present an 11 years old boy who referred to our clinic because of headache, hypertension, muscle weakness and muscle pain, and impaired walk. The present disease started one week before. Medical history showed a dysphonic speech from the age of six, treated with speech occupying therapy.

On admission he was conscious, afebrile and with gait disturbance with slight right-sided hemiparetic gait. During neurological examination verbal and visual contact was established, had dysarthric speech, no dysmetria, tandem gait was impossible to assess, negative Romberg test, Gowers test impossible to execute, cranial nerve examination revealed paresis of the left peripheral facial nerve, muscular tone was normal, muscular strength was normal in the left limbs while it was slightly reduced in the right limbs, tendon reflexes were preserved in the upper limbs with a hypoactivity in the lower limbs more designated on the right limb and positive incomplete Babinski sign on the right, superficial sensibility was preserved while deep sensibility for space was impaired, pathological involuntary movements were not observed and there were no meningeal signs.

Laboratory evaluation and diagnostic procedures were performed. Initial laboratory tests such as CBC, CRP, basic metabolic panel, lipid panel and liver panel revealed normal findings. Additional laboratory tests performed such as AFP level was with normal value, c-ANCA, ANA, Anti dsDNA were not found in serum, IEP serum test revealed normal results (Table 1 and Table 2).

Table 1: Laboratory values in blood

Blood	Value	Reference value
White blood cells (WBC)	**5.06**	3.5 – 10 x 10^3/uL
Platelets (PLT)	**254**	150 – 400 x 10^3/uL
Red blood cells (RBC)	**5.24**	3.5 – 5.2 x 10^6/uL
CRP	< **0.2**	0 – 5 mg/L
Glucose	**5.97**	4.1 – 5.9 mmol/l
Iron	**24.1**	6.6 – 26 umol/l

Feritin	**103**	30 – 400 ug/l
Transferin	**300.34**	130 – 360 mg/dl
AST	**22**	15-59 U/L
ALT	**6**	9 – 72 U/L
GGT	**15**	0 – 36 U/L
LDH	**183**	0 – 500 U/L
Total Bilirubin	**10.7**	3 – 22 umol/L
Direct Bilirubin	**5.1**	0 – 5 umol/L
Amylase	**133**	25 – 125 U/L
Lipase	**23**	8 – 78 U/L
Urea	**5.2**	2.6 – 6.4 mmol/L
Creatinin	**63**	0 – 104 umol/L
Albumin	**46**	40- 49 g/L
Total proteins	**69**	64 – 83 g/L
CK	**69**	29 – 200 U/L
CKMB	**24.66**	0 – 24 U/L
IgA	**1.12**	0.63 – 4.84 g/L
IgM	**1.19**	0.22 – 2.93 g/L
IgG	**8.19**	5.40 – 18.22 g/L
Total T3	**169**	82 – 179 ng/dL
TSH	**0.969**	0.4 – 4.0 uIU/mL
Total T4	**10.7**	4.5 – 12.5 ug/dL
Triglycerides	**0.59**	0 – 2.3 mmol/L
Cholesterol	**3.64**	0 – 5.2 mmol/L
UHDL	**1.4**	1.04 – 1.55 mmol/L
DLDL	**2.28**	2.59 – 4.11 mmol/L

Lactate	**2.11**	0.5 – 2.2 mmol/L
Sodium	**136**	135 – 145 mmol/L
Potassium	**3.79**	3.6 – 5.2 mmol/L
Ionised Calcium	**1.21**	1.15 – 1.30 mmol/L
Chloride	**101**	96 – 106 mmol/L
Vitamine B12	**294**	187 – 883 pg/mL
Uric acid	**346**	155 – 480 umol/L
D-dimer	**1962**	0 – 500 ng/mL
Prothrombin time (PT)	**14.7**	9.8 – 14.2 s
Activated partial thromboplastin time (aPTT)	**29.6**	27.9 – 37.7 s
Thrombin time	**17.9**	16.1 – 24.1 s

Table 2. Antibodies in blood

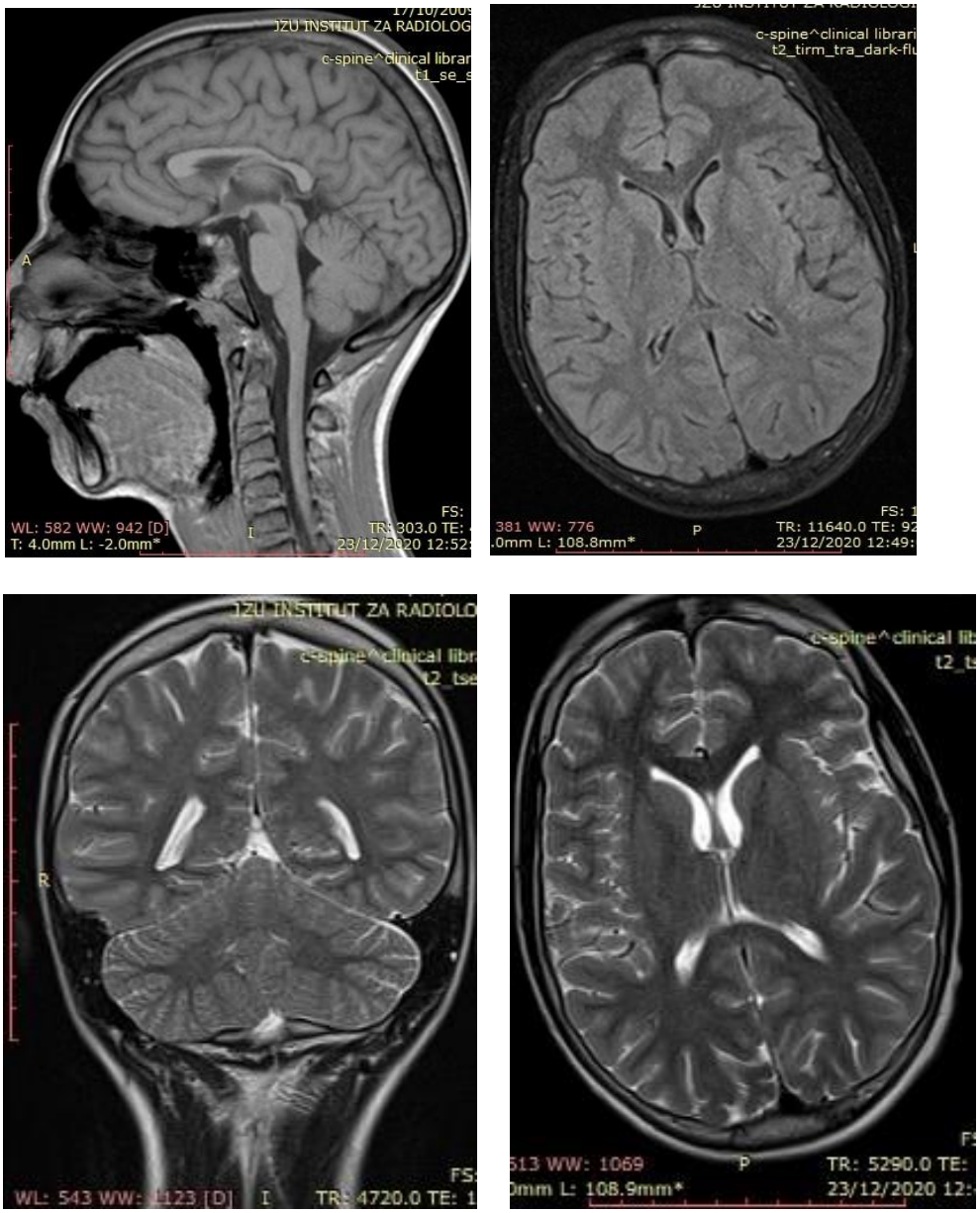
Antibodies (Blood) *	Value	Reference value
antiCCP	**negative**	< 25 IU/ml
ANA-Hep2(IFA)	**negative**	
antidsDNA	**negative**	< 55 IU/ml
Anti-Sm	**negative**	< 25 U/ml
c-ANCA	**negative**	< 5.0 U/ml
ACL-IgG	**negative**	< 10 U/ml
antiSSA	**negative**	< 12.5 U/ml
antiSSB	**negative**	< 12.5 U/ml
antiScl-70	**negative**	< 12.5 U/ml
AFA	**negative**	< 15 U/ml
ACLA IgM	**negative**	

*AntiCCP = anti cyclic citrullinated peptide; ANA-Hep2(IFA) = Anti-Nuclear Antibodies HEp-2(indirect fluorescence assay); antidsDNA =_anti-double stranded DNA; Anti-Sm= Anti-

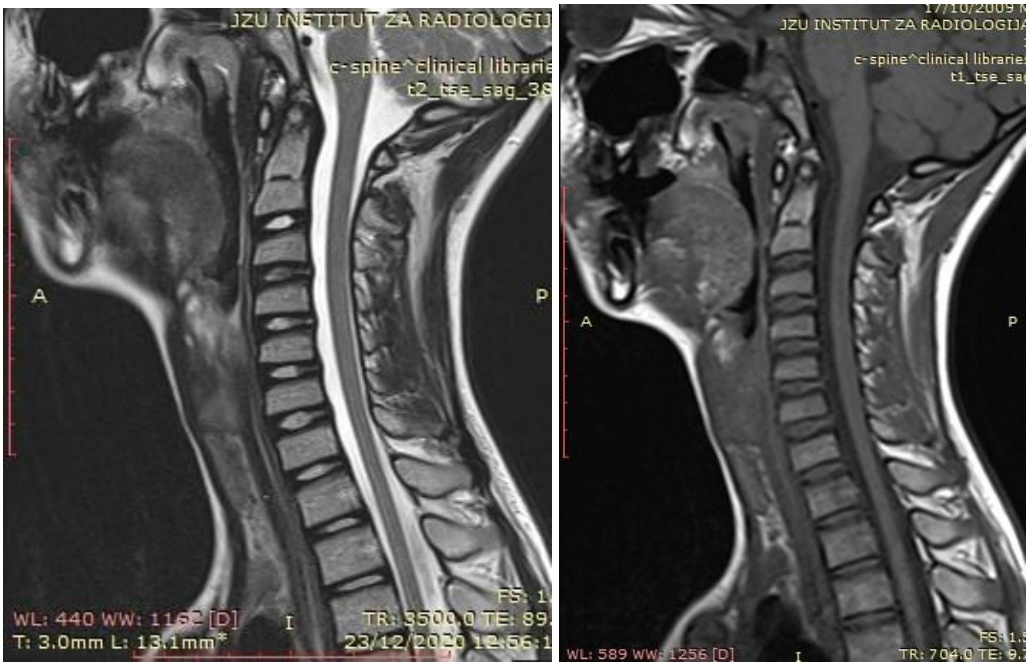
Smith antibodies; c-ANCA= antineutrophil cytoplasmic antibodies; ACL-IgG= Anti-cardiolipin autoantibodies- IgG; antiSSA= anti–Sjögren's-syndrome-related antigen A autoantibodies; antiSSB= Anti-Sjögren's syndrome type B (SSB) antibodies; antiScl-70= Autoantibodies against topoisomerase I; AFA= anti-fibrillarin antibodies; ACLA IgM= IgM anticardiolipin antibodies.

Abdominal ultrasound, chest X-ray, fundoscopic examination, brain CT scan and brain and spinal cord MRI revealed normal findings (Picture 1 and Picture 2). Electroencephalography (EEG) activity was normal, no epileptic activity nor cerebral dysfunction was recorded in the tracing (Picture 3). EMNG revealed normal findings.

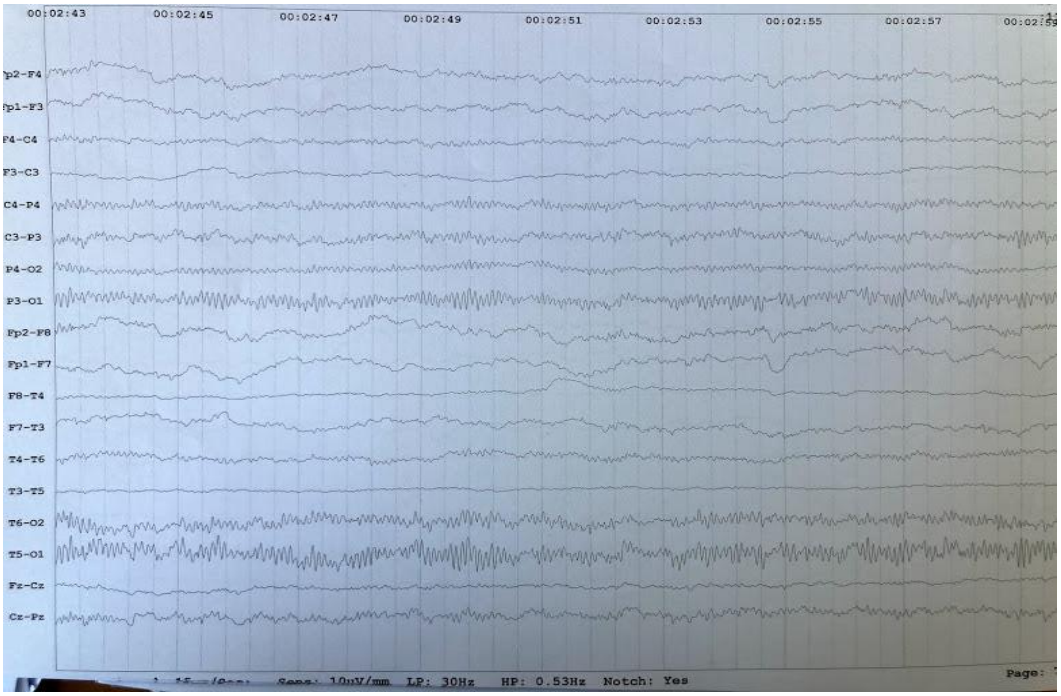
Picture 1. T1W, T2W and FLAIR Brain MRI sample images.



Picture 2. T1W and T2W cervical spinal cord MRI sample images



Picture 3. EEG sample of the patient



Lumbar puncture was done (Table 3) and electrophoretic separation of CSF proteins (Table 4) showed a total proteins content of 3.79 g/l, albumin content of 3260 mg/l and Immunoglobulin: IgG

of 237 mg/l with a IgG index of 0,3 x 10^{3} and IgG synthesis in CNS was 0 mg/24 h. According to the characteristics of the electrophoregram there is an immunological activity in the brain that corresponds to dysfunction of the hemathoencephalitic barrier with stressed compressive characteristics.

Table 3. Laboratory values in CSF

CSF	**Value**	Reference value
Appearance	**Clear**	clear
Glucose	**4.4**	2.7 – 4.1 mmol/L
Red blood cells	**0**	0
White blood cells	**0**	0 – 6 x 10^{6}/L
Protein	**3.79**	0.15 – 0.45 g/L
Albumin	**3260**	50 – 250 mg/L
Albumin coefficient	**59.50**	0.8 – 7.4 x 10^{3}
IgG	**237**	3 – 30 mg/L
IgG index	**0.3**	0.1 – 0.7 x 10^{3}
Chloride	**134**	116 – 127 mmol/l
Lactate	**1.9**	1.1 – 2.4 mmol/l

Table 4. Electrophoregram

CSF	Results	Value ranges
Total proteins (g/l)	3.79	0.15-045
Albumins(mg/l)	3260	50-250
IgG(mg/l)	237	3-30
Albumins coefficient (10^{3})	59.5	1.8-7.4
IgG index (10^{3})	0.3	<0.7
IgG synthesis in CNS (mg/24h)	0	<5

Two days after the admission ataxic gait was observed and a positive Romberg test with falling to the right.
Regarding hypertension pediatric cardiologist, nephrologist and endocrinologist were consulted. Renal artery Doppler ultrasound showed normal findings. 24 h Holter monitoring was done, which revealed normal findings. All laboratory findings were in normal range (Table 5). The hypertension was treated with antihypertensive drugs and it was stabilized in a few days.

Table 5. Laboratory values in urine

Urine	Value	Reference value
Metanephrin	**1.0**	< 5.5 umol/day (U)
Vanilmandelic acid (VMA)	**14.6**	7.0 – 68 umol/day (U)
Diuresis	**1.7 L**	0.8 – 1.5 L
Amylase	**291**	24-400 U/L

The findings from the COVID-19 specific IgG showed an elevated range of 52.59 AU/ml (Table 6).

	Value	Reference value
COVID-19 RBD (Receptor-Binding Domain) IgG	**52.59**	< 1.00 AU/mL

Treatment was implemented with intravenous immunoglobulins during five days with a dose of 400 mg/kg bw/day. He made a dramatic improvement over the next few days and was able to walk well and was fully recovered at the end of the second week.

Discussion: There are very few cases in the children and adolescents who have experienced neurological post COVID-19 complications. Our report is among the rarest with cerebellar ataxia-like and polyneuritis -like signs symptoms.
The affected child had no history of change or loss of taste and smell, nor the other specific COVD-19 symptoms. The only proof of past infections were the elevated COVID-19 specific IgG.
The results from the foregram with elevated proteins and immunoglobulins were indicating Guillain Barre Syndrome and electromyoneurographic findings were normal, but the clinical signs were indicating polyneuropathy.
Other possible infections which might give these neurological sign and symptoms were excluded with normal findings.

Conclusion: Although common symptoms of COVID-19 in children are cough and fever, it is important to note, however, that these symptoms may not always be present [12, 13, 14] or they may go unnoticed. The vast majority of reported infections in children are mild or asymptomatic, with few

recorded childhood fatalities attributed to covid-19 [2, 3, 4, and 5]. Additionally, there are few cases in pediatric population where post-COVID-19 complications emerge and need in-patient treatment. Currently, as we are still experiencing the pandemic and its effects, it is too early to describe the full clinical picture of PCNS. However, we believe published evidence has already made an undeniable case for medicine to recognize the increasing numbers of ex-patients with Post COVID Neurological Syndrome (PCNS) and the need for on-going neurological and cognitive/affective monitoring of all cases of COVID-19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS [15,16].

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ОПЫТ ПРИМЕНЕНИЯ ТРАНСФЕР ФАКТОРА ПРИ БРОНХИАЛЬНОЙ АСТМЕ НА ФОНЕ ДИСБАКТЕРИОЗА КИШЕЧНИКА

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Актуальность: В последние годы наблюдается нередкое сочетание болезней органов дыхания и пищеварения, что создает дополнительные трудности при обосновании комплексной терапии. В связи с этим, актуально выявление факторов риска развития дисбактериоза кишечника у различных категорий больных бронхиальной астмы для уточнения значения состояния кишечного микробиотопа в механизме развития рассматриваемой патологии.

По данным некоторых исследователей в 22-93% случаев бронхиальная астма протекает на фоне дисбактериоза кишечника. Нарушение микробиоценоза кишечника является не только как сопутствующим синдромом, отягощающий течение бронхиальной астмы, но и как важное звено в ее патогенезе. Особенностью современного течения бронхиальной астмы является нарастание тяжести заболевания, меньший эффект от проводимой терапии, увеличение длительности заболевания и числа летальных исходов. Применение гормонотерапии может привести у этих больных к развитию кишечного дисбактериоза, который способствует аллергизацию организма условно-патогенной кишечной флорой.

В настоящее время на рынке появилась новая биологически активная добавка, привлекшая к себе внимание клинических иммунологов, аллергологов и иммунологов.

Компания 4 Life Research (США) предлагает продукт, полученный из молозива особым способом ультрафильтрации и содержащий в своем составе высококонцентрированные факторы переноса – низкомолекулярные белки, обладающие иммуномодулирующими свойствами.

Цель исследования: Нашей целью явилась восстановление нормальной микрофлоры кишечной микрофлоры у больных бронхиальной астмой и исследование иммунного статуса.

Материалы и методы исследования: Больным назначали Трансфер Фактор, который зарегистрирован как БАД и разрешен к применению как универсальное корригирующее средство нормальной микрофлоры кишечника, применяется также для профилактики и лечения заболеваний желудочно-кишечного тракта.

Основной функцией факторов переноса (клеточных медиаторов) в организме является обеспечение иммунной защиты от патогенной микрофлоры, раковых клеток и других антигенных веществ, способных нарушать жизненно важные процессы в организме.

Результаты исследования: Отмечено, что «Трансфер Фактор», предлагаемы компанией 4 Life, стимулирует клеточное звено иммунной системы, в частности, лимфоциты-киллеры, активирует выработку иммуноцитокинов, регулирует функцию иммунитета.

Как отмечает академик РАМН А. А. Воробьев, достоинством «Трансфер Фактора» перед другими иммуномодуляторами, в том, что он обладает широким спектром действия,

абсолютно безопасен и безвреден, применяется перорально, не имеет противопоказаний к применению, не вызывает побочных действий, одинаково эффективен для взрослых и детей. Являясь универсальным иммунокорректором, трансфер фактор индуцирует или ослабляет иммунный ответ.

Имеющиеся литературные данные свидетельствуют, что трансфер фактор уже многие годы успешно используется для профилактики и лечения бактериальных, вирусных, грибковых инфекций, опухолей; при аутоиммунных, аллергических расстройствах; при иммунодефицитных состояниях.

Важно отметить, что перспективным является возможность сочетанного применения «Трансфер Фактора» и других иммуномодулирующих и адаптогенных препаратов у больных бронхиальной астмой на фоне дисбактериоза кишечника. Предварительное применение данного препарата с последующим включением в комплексное лечение других адаптогенов позволит направить их иммуномодулирующий эффект по пути выработки цитокинов и антител.

Назначение высокоочищенных компонентов молозива у больных с бронхиальной астмой позволит активизировать направленный иммунный ответ с выработкой высокого титра специфических антител и предупреждением нежелательных атопических реакций. С этих позиций для терапевтов представляют особый интерес основные компоненты трансфер-факторов от компании 4 Life. Это, прежде всего, фактор супрессии, способствующий регулированию интенсивности иммунного ответа Т-супрессоров, контролирующих атопические и аутоиммунные реакции.

Отмечено, что антиген-презентирующий компонент трансфер -фактора значительно снижает период выработки антител, ускоряя представление антигенов иммунокомпетентым клеткам.

Известно, что зачастую персистирование хронической инфекции связано с отсутствием адекватной фагоцитирующей и переваривающей возможности макрофагов, что значительно удлиняет период презентации чужеродных антигенов Т-лимфоцитам и последующей выработки антител.

«Трансфер Фактор» является гипоаллергеным продуктом, так как полностью очищен от козеина, лактоглобулинов и других крупных белковых молекул и оставлены цитокиновые фракции, идентичные лейкоцитарным цитокинам.

Мембранная патология, способствующая высокой адгезии патогенной флоры и началу инфекционного процесса, часто протекает на фоне предшествующей нестабильности цитомембран и усиления внутриклеточных свободнорадикальных процессов.

Многочисленные клинические испытания, проведенные в России и Казахстане и других странах по эффективности применения трансфер-фактора у больных позволили выявить и другие аспекты его действия.

Наряду с иммуномодулирующим эффектом, отмечены антиоксидантные и мембраностабилизирующие эффекты трансфер-фактора. Эти данные открывают новые перспективы комплексного применения трансфер-факторов с другими иммуномодулирующими препаратами. Сочетанное их применение могут быть с успехом использованы в сезонной профилактике обострений и возникновения приступов бронхиальной астмы.

Пероральный путь применения трансфер-фактора, в отличие от иммуномодулирующих средств, которые необходимо ввести парэнтерально, позволяет использовать его в

поликлинических условиях с целью профилактики и иммунореабилитации в группах риска и у больных бронхиальной астмой.

Многочисленные зарубежные данные, а также клинические испытания, проведенные в нашей стране, свидетельствуют о высокой эффективности трансфер-факторов у больных с тяжелыми вирусными инфекциями (СПИД, вирус гепатита С, вирус Эпштейн-Бера и др.), с онкологическими заболеваниями.

Представляется перспективным использование трансфер-факторов больных с бронхиальной астмой при инфекции желудочно-кишечного тракта, при дисбиозах кишечника. Снижение свободно-радикального окисления липидов и повышение стабильности цитомембран оказывает протекторное действие на эпителиальный покров слизистых, увеличивая тем самым конкурентную адгезию на них полезной микрофлоры, и усиливая локальный иммунитет. Трансфер фактор может быть использован в комплексе с про- и эубиотиками, гепатопротекторными, противовирусными препаратами.

Выводы: Таким образом, имеются широкие возможности применения перорального варианта трансфер-факторов в практике с бронхиальной астмой на фоне дисбактериоза кишечника с профилактической целью.

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EXPERIENCE IN THE USE OF TRANSFER FACTOR IN BRONCHIAL ASTHMA AGAINST THE BACKGROUND OF INTESTINAL DYSBIOSIS

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Relevance: In recent years, there has been a frequent combination of respiratory and digestive diseases, which creates additional difficulties in justifying complex therapy. In this regard, it is important to identify risk factors for the development of intestinal dysbiosis in various categories of patients with bronchial asthma to clarify the significance of the state of the intestinal microbiotope in the mechanism of development of this pathology.

The aim of the study: Our goal was to restore the normal intestinal microflora in patients with bronchial asthma and to study the immune status.
Materials and methods of research. Patients were prescribed Transfer Factor, which is registered as a dietary supplement and is allowed for use as a universal corrective agent of normal intestinal microflora, it is also used for the prevention and treatment of diseases of the gastrointestinal tract. The main function of transfer factors (cellular mediators) in the body is to provide immune protection against pathogenic microflora, cancer cells and other antigenic substances that can disrupt vital processes in the body.

The results of the study: It is noted that the "Transfer Factor", offered by the company 4 Life, stimulates the cellular link of the immune system, in particular, killer lymphocytes, activates the production of immunocytokines, regulates the function of immunity. As Academician of the Russian Academy of Medical Sciences A. A. Vorobyov notes, the advantage of "Transfer Factor" over other immunomodulators is that it has a wide spectrum of action, is absolutely safe and harmless, is used orally, has no contraindications to use, does not cause side effects, is equally effective for adults and children. As a universal immunocorrector, transfer factor induces or weakens the immune response.

Conclusions: Thus, there are wide possibilities of using the oral version of transfer factors in practice with bronchial asthma against the background of intestinal dysbiosis for preventive purposes.

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