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ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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Allergic bronchopulmonary aspergillosis (ABPA) should be considered in patients with poorly controlled asthma despite appropriate routine therapy and environmental control. The need for frequent courses of corticosteroids with temporary improvement should raise the index of suspicion and appropriate evaluation be done. Early recognition and prompt initiation of appropriate corticosteroid treatment regimen would reduce the risk of development or progression of bronchiectasis and lung tissue damage. Regular follow up and monitoring serum total IgE level can predict exacerbations and should prompt corticosteroid treatment. Long term follow-up is important as relapses can occur years of remission.

Key words: *allergic bronchopulmonary aspergillosis, allergic pulmonary mycosis, uncontrolled asthma, asthma, cystic fibrosis, bronchiectasis, aspergillus.*

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Abbreviations: ABPA=allergic bronchopulmonary aspergillosis, ABPM=allergic bronchopulmonary mycoses, CFTR=cystic fibrosis transmembrane conductance regulator, HRCT=high resolution computed tomography, EOD=every other day.

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Micheli first described the mold aspergillus in 1729 as it looks like aspergillum, the Latin term for a device used to sprinkle Holy water [1]. Bennett was the first physician to describe pulmonary aspergillosis as "numerous jointed transparent tubes, here matted together, there isolated…mingled with round or oval corpuscles, which, however, were larger and more developed" [2]. Later, Fresenius described *Aspergillus fumigatus* as having "green pigmentation with no fertile septate hyphae or conidiophores". The word fumigatus means smoky in Latin, referring to the fungus' smoky blue-gray color. An association with human disease was first described in 1847 of a woman dying with an unspecified lung infection [3]. Virchow described four cases of pulmonary aspergillosis in patients dying of other conditions in 1856. In 1887, Osler reported the case of a young woman who coughed up sputum for eleven years of mycelia and spores of aspergillus. In 1897, Renon was the first to associate aspergillus with asthma and that same year, Brown and Feinberg noted that between 1 and 20% of patients with asthma have positive skin tests to aspergillus extract [4]. The first report of allergic bronchopulmonary aspergillosis (ABPA) was proposed by Hinson et al in 3 patients in 1952, all of whom were asthmatics presenting with persistent wheeze, sputum production, fever, eosinophilia and pulmonary infiltrates. ABPA can be caused by a variety of aspergillus species, most commonly *A. fumigatus* but other species have been implicated including *A. niger*, *A. flavus*, *A. nidulans*, *A. oryzae*, *and A. terreus* [5].

Aspergillus is a saprophytic mold and its natural habitat is the soil [5]. It is found worldwide indoors and outdoors in potted soil, compost, freshly cut grasses, decaying vegetation and in sewers. Aspergillus produces a bountiful number of spores and releases 2–3 micron sized spores into the air daily [6]. It grows best at 37–40°C, which is similar to the temperature in the lungs. These spores will remain airborne for a long period of time. It is estimated that humans inhale hundreds of spores daily.

Several fungi other than aspergillus have been known to be implicated. Hence, the term allergic bronchopulmonary mycoses (ABPM) would be more appropriate unless the specific fungus is identified – which could be candida, helminthosporium, curvularia, bipolaris, cladosporium, or others. In this review article, we will focus on the prototype ABPA.

Epidemiology

The exact prevalence of ABPA is unknown. It depends on a variety of factors including the severity of asthma, presence of immediate hypersensitivity to aspergillus, method of detection, and the diagnostic criteria used. It is estimated to affect about 2% of asthmatics and 1–15% of cystic fibrosis patients [7], without gender predilection. Typically, it affects asthma patients in their third or fourth decade [8].

Pathogenesis

Based mainly on *in-vitro* studies, multiple theories have been proposed regarding the pathogenesis of ABPA.

The most common theory suggests that in patients with asthma and cystic fibrosis who are genetically predisposed

and have increased pulmonary mucus viscosity, the inhalation of aspergillus spores causes colonization and deposition of the hyphae [9]. These hyphae release antigens which are disruptive to the epithelial barriers impeding mucociliary clearance. This results in the attraction of inflammatory cells that in turn release cytokines causing inflammation. The process is hypothesized to have a Th2 cell predominance over Th1 cell causing a release of IL-4, IL-5, and IL-13, resulting in eosinophilia and elevation of IgE [10]. The influx of these inflammatory cells is directly involved in tissue destruction. In the lungs, this can cause central bronchiectasis.

A second hypothesis is based on the findings of a study by Garcia et al who reported a different pattern of cellular responses in individuals with ABPA than those with only allergic asthma [11]. They observed a downregulation of chemokine receptors CCR4 and CXCR3 *in vitro* by allergen specific CD4+ T cells of ABPA patients, which is opposite to the effect in patients with only allergic asthma.

A third hypothesis is by Miller et al for cystic fibrosis patients suggesting that the cystic fibrosis transmembrane conductance regulator (CFTR) gene has a greater chance of mutating compared to healthy controls [12].

The pathogenesis of ABPA is attributed to mucoid impaction of the bronchi with fungal hyphae, eosinophilic pneumonia or bronchitis, and bronchocentric granulomatosis with tissue eosinophilia [13]. In the airways, septated hyphae with acute dichotomous branching is seen in the lumen without invasion of the mucosa. Aspergillus is found in sputum cultures in two thirds of patients although often is not seen by microscopy. Key findings in sputum are Curschmann spirals (mucus plugs) and eosinophilic debris (Charcot–Leyden crystals) [14].

Diagnosis and evaluation

The diagnosis of ABPA should be based on clinical suspicion and supported by radiologic and laboratory findings. An important clinical feature of the presentation of ABPA is deterioration of pulmonary symptoms with increased wheezing and shortness of breath. These patients typically present with fever, malaise, productive cough with brownish mucus plugs, and occasionally hemoptysis[15].

The diagnosis is typically suspected in patients with recurrent asthma or cystic fibrosis exacerbations. It is important to rule out other causes before committing to the diagnosis of ABPA. Other causes of bronchiectasis could be post infection, immunodeficiency, or ciliary dysfunction. Several other causes of eosinophilia should also be considered such as eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, hyper eosinophilic syndrome, hypersensitivity reactions, and parasitic infections.

In general, the evaluation should consist of obtaining a complete blood count, skin prick test to aspergillus, specific IgE to aspergillus, serum precipitins (or IgG antibody) to aspergillus, chest x-ray, and a high resolution computed tomography (HRCT) of the lungs [16]. If the skin prick test is negative, intradermal testing can be considered. In general, specific IgE to aspergillus alone suggests sensitization only which is not diagnostic of ABPA and is frequently present in patients with severe eosinophilic asthma. Total serum IgE should be obtained as this is useful during monitoring.

ABPA (or ABPM) should be considered among the cases of poorly controlled asthma or cystic fibrosis. Currently, the most widely accepted criteria are those proposed by Rosenberg and Patterson [17]. In patients with asthma, the severity of their condition does not determine diagnosis. If most of the criteria presented in Table 1 are met, there is a high clinical suspicion of ABPA [18]. Those criteria were later revised by Greenberger who reported that only asthma, immediate skin hypersensitivity to aspergillus, total serum IgE>1000 ng/mL (>417 IU/mL) and central bronchiectasis in the absence of distal bronchiectasis is required for the diagnosis [19]. Since central bronchiectasis is not required for diagnosis, some suggested that patients can be categorized into subgroups: ABPA-Seropositive and ABPA-Central bronchiectasis [20]. Agarwal and coworkers proposed that all patients diagnosed with asthma must be screened for specific IgE levels to aspergillus [21]. If negative, total IgE levels and sensitization to other fungi should be obtained to rule out ABPM. In patients sensitized to aspergillus, total IgE levels below 1000 IU/mL and uncontrolled asthma suggest severe asthma with fungal sensitization as an alternative to ABPA. This subset of patients may benefit from anti-fungal therapy. In patients with fungal sensitization to aspergillus and a total IgE level greater than 1000 IU/mL, clinicians should obtain eosinophil levels, immediate skin hypersensitivity, and specific IgG to aspergillus. If any two of the criteria are positive, ABPA is confirmed and HRCT should be performed for staging of the disease. Although some authors suggest a significantly higher total serum IgE level of 1000 IU/mL (2400 ng/mL) for diagnosis [22], most authors follow the 1000 ng/mL (417 IU/mL) as a cutoff level. Table 2 shows the diagnostic criteria of ABPA in patients with cystic fibrosis [17].

Table 1

Diagnostic criteria for ABPA in asthmatics

Major Criteria	*Minor Criteria*
• Chronic asthma • Transient pulmonary infiltrates (fleeting) • Immediate cutaneous hypersensitivity to aspergillus species • Elevated total serum IgE > 1000 ng/mL (417 IU/mL) • Precipitating antibodies to aspergillus species • Blood eosinophilia • Elevated serum specific IgG and IgE to aspergillus • Central/proximal bronchiectasis	• Golden brown mucus sputum production • Sputum positive for aspergillus • Late skin reactivity to aspergillus species

Adapted from Rosenberg and Patterson [18].

Testing for IgG antibodies to aspergillus species (or other suspected molds) is performed by ELISA assay which replaced testing for precipitins by gel immunodiffusion [6]. Pulmonary function testing is valuable in monitoring the disease severity but not for the diagnosis of ABPA17. Spirometry typically shows an obstructive pattern but can also develop restriction in late stages of the disease. After treatment

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with corticosteroids or during remission, a normalization of these parameters often occurs.

Table 2

Criteria for ABPA in cystic fibrosis patients

Presence of 2/3 criteria	*PLUS*	*Presence of 2/6*
• Immediate skin hypersensitivity to aspergillus species • Precipitating antibodies to aspergillus species • Total serum IgE > 1000 IU/mL		• Bronchoconstriction • Peripheral blood eosinophilia > 1000/μL • Chest x-ray abnormalities (infiltrates, bronchiectasis) • Elevated serum specific IgE and IgG to aspergillus species • Aspergillus in sputum • Response to systemic corticosteroids

Modified from Shah and Panjabi [17].

Table 3

Staging of ABPA

Stage I: Acute	• Normal radiographic features or pulmonary infiltrate with mucoid impaction especially in the upper lobes
Stage II: Remission	• Radiologic infiltrate clears • Decreased in total serum IgE and eosinophilia • Prednisone tapered and goal to discontinue
Stage III: Exacerbation	• Reappearance of infiltrates and mucoid impaction in previously cleared areas or in new ones • Restart treatment with prednisone
Stage IV: Corticosteroid-dependent asthma	• Glucocorticoid-dependent with return of symptoms if tapering or discontinuation is attempted • Normal chest radiography or fixed pulmonary opacities are visualized
Stage V: Fibrotic	• Permanent lung damage (i.e. bronchiectasis, pulmonary hypertension)

Modified from Greenberger and Patterson [24].

Radiologic features and staging

Chest x-ray and often HRCT are recommended during evaluating patients for ABPA. Chest x-ray can show transient changes such as fleeting patchy areas of consolidation [17]. The infiltrates can appear as gloved finger shadows due to mucoid impaction in dilated bronchi. It can also present as a lobar or segmental atelectasis. When permanent changes occur, parallel-line shadows representing bronchial widening and ring shadows approximately 1–2 cm in diameter may be visualized. Additionally, it can be accompanied by pulmonary fibrosis.

High resolution chest tomography can reveal a variety of parenchymal findings including central bronchiectasis, consolidation, centrilobular nodules with tree-in-bud opacities, bronchial wall thickening, mosaic attenuation, and areas of atelectasis23. A characteristic finding of ABPA is bronchiectasis of greater than two lobes at lobar and segmental levels in a majority of the airways [14].

Based on radiologic features, criteria have been incorporated in classifying the stages of ABPA (Table 3). Five stages have been described: acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic [24]. Patients can initially present at any stage. Although the common age for ABPA is young and middle-aged adults, children are not exempt, as illustrated in the following case.

Case presentation

One of our patients was a 12-year-old female with a history of eczema and persistent asthma since early childhood. At 8 years of age, she had a severe asthma exacerbation that required admission to the intensive care unit for impending respiratory failure. Since 10 years of age, in spite of adequate routine asthma therapy, she had many exacerbations requiring frequent emergency treatment and five hospitalizations. There were no apparent triggers of the exacerbations She was on combined fluticasone/salmeterol 230 mcg/21 mcg 2 puffs twice daily, loratadine 10 mg in the morning and montelukast 10 mg at bedtime. However, she experienced a worsening of her asthma and a decline of her flow function on spirometry despite strict adherence to medications. She had persistent wheezing that required the intake of albuterol inhaler 3–4 times daily. She also received prednisone courses numerous times, including more than ten times during the past year, with improvement for short durations. During the recent hospitalization, the Allergy/Immunology service was consulted. Her CBC was within normal limits, including absolute eosinophil count (100/μL) but the test was done while she was on systemic corticosteroid administration. Her serum total IgE level was 2040 IU/mL raising suspicion of ABPA. Serum specific antibodies to aspergillus were elevated for both IgE (28.5 IU/mL) and IgG (23.7 IU/mL). Chest X-ray showed bilateral hyperinflation, streaky atelectasis in the right middle lobe, and peribronchial cuffing. HRCT of the lungs did not show any infiltrates or bronchiectasis. She did meet the majority of ABPA criteria and was treated with 40 mg prednisone daily until follow up in the clinic. At follow up after two weeks, she reported marked improvement in her asthma symptoms, but continued to experience nocturnal chest tightness and coughing. Her spirometry revealed a FEV_1 1.23 L (53%), FVC 2.10 L (81%), FEV_1/FVC 59%, and FEF 25–75% 0.56 L/s (18%). Her IgE level dropped to 1350 IU/mL. Her eosinophil count was very low due to prednisone intake. The prednisone dose was reduced to 40 mg every other day (EOD) and beclomethasone dipropionate 1 puff twice a day was added to her regimen to improve small airway inflammation. After one month, she reported dramatic improvement in her symptoms and minimal nocturnal symptoms. Repeat spirometry showed a FEV_1 1.95 L (81%), FVC 2.45 L (92%), FEV_1/FVC 80%, FEF 25–75% 1.80 L/s (51%). Her IgE level remained relatively stable at 1410 IU/mL. Due to subjective and objective improvement, her prednisone was decreased to 30 mg EOD until follow-up in two weeks. The drop of her initial IgE level from 2040 IU/mL to 1220 IU/mL after four

months was associated with improvement in her FEV_1 from 59% predicted to 81% predicted. She will continue regular follow up in the clinic and gradually reduce the prednisone dose according to her clinical course.

Treatment

The primary goals of treatment are to prevent the development or progression of bronchiectasis, preserve lung function, and improve pulmonary physiology. In general, inhaled corticosteroids are ineffective in preventing acute ABPA episodes [15]. Oral corticosteroids are the mainstay of therapy [25]. It is recommended to complete a minimal of three months of treatment starting with prednisone 0.5 mg/kg/day for two weeks, then alternate days for three months followed by staging of the disease. Some experts start at a higher dose at 0.75 mg/kg/day for 6 weeks, followed by 0.5 mg/kg/day for 6 weeks, and eventually taper over a period of 6–12 months to prevent disease recurrence [26]. There are no studies comparing regimens at this time, although most experts tend to favor longer therapy with higher dosages of prednisone [27]. Monitoring of total serum IgE level monthly is important in determining duration of treatment as well as in predicting pending relapse. In general, aiming for 35% reduction in IgE is suggestive of a good response and decreases the likelihood of relapse. It is important to consider the patient's clinical response, as occasionally the level of IgE does not drop by 35% when the initial total IgE is less than 2500 IU/mL [28].

In patients with corticosteroid-dependent ABPA, Stevens and coworkers reported clinical improvement with the use of 200 mg of itraconazole twice a day [29]. Liver function should be monitored regularly, and treatment is typically for three to six months although this varies depending on the response [30]. The mechanism of action is thought to be due to a decrease in antigenic stimulus that causes inflammation in the bronchi [31]. Another proposed hypothesis is that it causes increased levels of serum corticosteroids by interfering with the metabolism. A major concern is that adrenal suppression has been observed with concomitant use of corticosteroids and itraconazole [32]. Voriconazole and posaconazole have also been used and has improved tolerance and bioavailability [33], but there are no studies that showed superiority over itraconazole.

Anti-IgE (omalizumab) therapy using doses recommended for asthma, showed promising results with improvement in respiratory symptoms in patients with ABPA [34]. In one study, sixteen adult asthmatic ABPA patients were treated with omalizumab for one year and had clinical improvement with fewer asthma exacerbations and requiring lower doses of corticosteroids. Currently, omalizumab is based on weight and total serum IgE and majority of patients exceed the recommended dose range due to grossly elevated IgE14. Based on available data, it remains a second line option for patients with ABPA.

Immunotherapy with aspergillus or other fungi have not been fully evaluated and is currently not recommended for treatment [35]. Patients who are on immunotherapy for allergic rhinitis can continue treatment safely.

Conclusion

ABPA should be considered in patients with poorly controlled asthma despite appropriate routine therapy and environmental control. The need for frequent courses of corticosteroids with temporary improvement should raise the index of suspicion and appropriate evaluation be done. Early recognition and prompt initiation of appropriate corticosteroid treatment regimen would reduce the risk of development or progression of bronchiectasis and lung tissue damage [36]. Regular follow up and monitoring serum total IgE level can predict exacerbations and should prompt corticosteroid treatment. Long term follow-up is important as relapses can occur years of remission.

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SEMAPHORIN 3A IS HIGHLY BENEFICIAL IN TREATING BRONCHIAL ASTHMA: REDUCING BOTH INFLAMMATION AND ANGIOGENESIS

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Semaphorin 3A (sema3A) belongs to a big family of immune semaphorins, whose main role is the regulation of immune-mediated inflammation. It was shown to be expressed on both T and B regulatory cells, and as such is a useful marker for evaluating their functional status. In our earlier study, we reported on reduced sema3A expression on Treg cells and in the serum of asthma patients, in correlation with asthma disease severity. When Treg cells were stimulated with recombinant sema3A, we could see a significant increase in FoxP3 and IL-10 expression. As a result, we evaluated the efficacy of sema3A injection into a mouse model of asthma. Thirty ovalbumin (OVA) sensitized WT BALB\c-mice were included in this study. Sensitization was performed using OVA+ adjuvant for 15 days followed by OVA aerosol inhalation. At this stage, the mice were divided into two groups: In 15 mice, 50 micrograms of recombinant purified human sema3A was injected four hours after OVA inhalation over five consecutive days. In the other 15 mice (control group) empty vector was injected according to the same regimen as above. At the end of the study, broncheo-alveolar lavage (BAL) and formalin-fixed lung biopsies were analyzed. In sema3A treated mice, only 20% of bronchioles and arterioles were infiltrated by inflammatory cells as compared to 90% in the control group (p=0.0079). Eosinophil infiltration was significantly increased in the control group; 25-35 eosinophils

per high power field (HPF) compared to only 5–7 eosinophils per HPF in the sema3A treated mice (P=0.028). Finally, in untreated mice, angiogenesis was significantly increased in comparison with sema3A treated mice as evidenced by the reduced number of microvessels in the lungs of sema3A treated mice. To conclude, we find that in this asthma model, sema3A is a potent suppressor of asthma related inflammation that has the potential of becoming new therapeutic tool for asthma.

Key words: *bronchial asthma, angiogenesis, inflammation.*

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Semaphorins are a big family of proteins, widely involved in angiogenesis, the spread of metastasis and the regulation of immune mediated inflammation. Their involvement in both innate and adaptive immune responses has labeled part of them as "immune semaphorins". Semaphorin 3A (sema3A), is mainly a secreted member of this family but also a membrane interacting molecule, which has been characterized as a regulator of immune mediated inflammation. In an early study, when sema3A was co-cultured with stimulated T effector cells it inhibited their proliferation and their ability to secrete pro-inflammatory cytokines [1]. Later, the expression of sema3A on Tregs from patients suffering from rheumatoid arthritis (RA) was found to be altered in association with increased disease activity. Taken together, these findings establish sema3A as a marker for Treg cells and as a target for therapeutic strategies. When recombinant sema3A was injected into collagen-induced arthritis (CIA) mice, Treg cell function was restored and RA disease activity in these mice was reversed [2]. Furthermore, we have also observed that the concentration of sema3A is reduced in serum of systemic lupus erythematosus (SLE) patients, and was correlated with SLE disease activity.

We further demonstrated the importance of sema3A to the etiology of SLE by injecting sema3A into NZB/W mice (an animal model of SLE). Indeed, sema3A injection reduced and delayed proteinuria and renal damage and increased survival of these mice [3]. In patients with active bronchial asthma, decreased amounts of Treg cells and altered expression of FoxP3 were found to be in association with increased level of Th17. In this case, dexamethasone therapy was shown to correct this disturbed balance between Treg and Th17 cells [4]. Chronic airway structural changes such as smooth muscle cells hypertrophy, and angiogenesis are consequences of long-lasting inflammation in bronchial asthma and are considered to be part of the remodeling process.

In contrast with the high beneficial effect of inhaled corticosteroids in reducing lung T cell and eosinophil infiltration, their effect on angiogenesis is still ill defined. With this in mind we initiated this study with the intention of evaluating the therapeutic immune-modulatory effects of sema3A when injected into an asthma mice model and to determine if it has a beneficial effect as an inhibitor of inflammation in the lungs of these mice. In addition, we are determined if sema3A can reduce the angiogenic hyperactivity seen in severe asthma and if this can be an additional mechanism by which sema3A can contribute to the treatment of asthma.

Material and Methods

Asthma mice model treated with recombinant human sema3A: 30 female Balb/c mice 6- to 7- old weeks were included in this study. OVA sensitization and airway challenge were performed as follows: the mice were sensitized intraperitoneally with 50 μg ovalbumin (OVA; grade V; Sigma-Aldrich) emulsified in 2 mg Alum-Hydroxide (Sigma-Aldrich) in 200 μl 0.9% sodium chloride (saline; Hospira) on Days 0, 7, and 14. On Days 22–25, the mice were placed in a box and were exposed for 20 minutes to an aerosol consisting of 1% (m\v) OVA dissolved in PBS, Ph-7.4. Four hours following air ways sensitization 15 of these mice were injected intraperitoneally with 50 μg per mouse of recombinant human sema3A and the remaining 15 mice were injected with v\v purified empty vector vehicle condition media (control), as described above. The mice were sacrificed after five days following termination of treatment (day 30). Bronchoalveolar lavage (BAL) was collected and lung tissue was taken for evaluation of treatment efficacy.

Results

1. The effect of sema3A treatment on the concentration of inflammatory cells in BAL: We determined the number of inflammatory cells in the BAL fluid in sema3A treated versus control groups. In the sema3A treated group, we could see only a small number of neutrophils, contrary to the control mice where BAL was highly enriched in neutrophils (p=0.03).

2. Effect of sema3A treatment on inflammation in lung biopsies derived from asthma mice: We analyzed the extent of inflammation in tissues surrounding the bronchioles and blood vessels in the lung and determined the number of eosinophils per HPF in these tissues. In sema3A treated mice, only 20–30% of the bronchioles and arterioles were infiltrated by inflammatory cells compared with 90–100% in the control group not treated with sema3A (p=0.0021). The infiltration of eosinophils was also more pronounced in the control group with 25–35 eosinophils per HPF as compared with only 5–7 eosinophils per HPF in the sema3A treated mice (p=0.033).

3. The anti-angiogenic effects of sema3A: Sema3A is known as a potent anti-angiogenic factor. We therefore, determined the effects of sema3A on angiogenesis by examination of lung biopsies. As expected, we detected an anti- angiogenic effect of sema3A treatment. In the vehicle-treated group the concentration of micro-capillaries was 10.22±2.178\HPF as compared to a concentration of 2.46±0.932 capillaries\HPF in lung biopsies derived from sema3A treated mice (p=0.0017).

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Discussion

Airway inflammation in bronchial asthma is classically characterized by multiple inflammatory pathways involving both innate and adaptive immune responses. The hallmark of this inflammation was always considered to be T-cell-driven, involving all T cell phenotypes. Increased IL-17 production was reported responsible for the neutrophil influx into airways as well as for the depletion of Tregs in peripheral blood and in inflamed airways of patients with bronchial asthma. IL-22 was also reported to be involved in airway hyper-reactivity and inflammation of OVA-sensitized mice. Lungs of these mice were infiltrated with $CD3^+CD4^+IL\text{-}22^+$T cells that co-expressed IL-17 and TNF-α in association with neutrophil airway infiltration [5, 6]. The new approach of improving the potential of regulatory pathways rather than using immunosuppressive agents (such as steroids and cytotoxic drugs), for treating immune-mediated inflammatory diseases is gaining popularity. In that respect, sema3A was recently reported to be a good candidate for this concept. In previous studies we demonstrated its beneficial effect in downregulating the increased expression of TLR-9 in activated B cells from both normal individuals and from patients suffering from SLE. These findings are in accordance with in-vivo studies in which the injection of recombinant sema3A effectively improved allergic rhinitis and atopic dermatitis in relevant mice models. The present study is the first to show that sema3A is highly beneficial in reducing the infiltration of both neutrophils and eosinophils in lung tissue inflammation and in BAL derived from OVA-sensitized mice. Long-lasting airway inflammation may lead to structural changes termed remodeling. These changes consist of sub-epithelial layer thickening, airway smooth muscle hyperplasia and increased angiogenesis. The increased formation of new blood vessels is a critical step in the process of angiogenesis and vascular remodeling, and is induced by the expression of angiogenic factors such as VEGF and angiopoietin. On-going angiogenesis in the alveoli of asthmatic patients is usually followed by tissue edema and increased vascular permeability which is also triggered by VEGF. Inhaled corticosteroids and anti-leukotriens are of limited influence on angiogenesis and remodeling in most cases [7, 8]. The timing of anti-angiogenic therapy is crucial in attenuating this process and preventing irreversible fibrosis. The beneficial effect of biological therapies such as the anti-IgE omalizumab and the anti-IL-5 mepolizumab on remodeling is still ill defined and remains to be assessed. Our study is unique in reporting on the highly beneficial effect of sema3A in reducing inflammation but also angiogenesis in bronchial asthma. Of the reported mechanisms by which sema3A inhibits angiogenesis, the most important is its high efficacy in inhibiting VEGF activity as a result of the activation of inhibitory intracellular pathways that inhibit VEGF signal transduction. This is the first study, in which sema3A is suggested to become a unique therapy for bronchial asthma. This unique compound is special in using its regulatory properties of action reducing by that neutrophil and eosinophil infiltration in BAL and lung tissues, but also in the likelihood of being a promising therapy in reversing increased angiogenesis and lung remodeling. Future studies should aim on strengthening these results by showing the benefit of this therapy in improving lung functions.

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PSYCHOSOMATIC ASPECTS IN FAMILY PRACTICE IN PATIENTS WITH GASTROENTEROLOGICAL DISEASES

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Depressive and anxiety disorders are common psychiatric illnesses. According to World Health Organization statistics, there were more over 350 Mln people suffering from depressive disorders worldwide in 2012, suggesting that depressive disorders have become an important source of the global burden of diseases. The digestive system is vulnerable to the influence of emotional factors, because its function is regulated mainly by the vegetative nervous system and the endocrine system, and the center of both systems has the same anatomical location as the subcortical integration center of the emotional center.

Key words: *gastroenterological diseases, depressive disorders, anxiety disorders*.

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Anxiety and depression are the two most common mental health problems in the general medical setting Although increasing attention has been paid to anxiety, it still lags far behind depression in terms of research as well as clinical and public health efforts in screening, diagnosis, and treating affected individuals. This is unfortunate given the prevalence of anxiety and its substantial impact on patient functioning, work productivity, and health care costs. Over 30 Mln Americans have a lifetime history of anxiety, and anxiety disorders cost an estimated $42 billion dollars per year in the United States alone, counting direct and indirect costs.

The four most common anxiety disorders (excluding simple phobias that seldom present clinically) are generalized anxiety disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder. However, despite the substantial disability associated with each anxiety disorder and the availability of effective treatments, only a minority of patients (15 to 36%) with anxiety are recognized in primary care

Depression is a negative emotional state that affects all of us to some degree. It can usurp our happiness and substantially diminish our quality of life. Depression can be conceptualized along a continuum ranging from mild sadness and lack of vivre to intense misery, despair, and unwavering desire to die. It frequently disrupts functional capacity and can result in poorer scholastic, vocational, interpersonal, and intimate functioning. Depressed persons frequently experience decreased energy levels, impaired attention and concentration, somatic complaints, and preoccupation with bodily concerns.

Combined treatment can diminish the likelihood of protracted psychologic suffering that can theoretically jeopardize job status, marital status, friendships, and even in the case of suicide, one's life.

The mind/body connection has become a popular topic in recent years, and many researchers have found that the mind and body influence each other more than previously thought. Recent studies have found positive correlations between a wide range of physical complaints, including Gastrointestinal (GI) problems, and trait anxiety disorders and depression. Many replications have supported this relationship using clinical populations, yet few replications focus on the general population.

Sharma, Ghosh and Spielberger (1995) found that men diagnosed with gastric ulcer had higher levels of trait anxiety than men without gastric ulcer.

Data on the prevalence of anxiety and depression in patients in general practice are different, but the numbers in all the studies are large enough. In the WHO multinational study of 14 primary case medical clinics, located in major cities around the world, psychological disorders were detected in 25% of those seeking treatment. Studies conducted in the U.S. showed that the proposition of patients' depression with somatic diseases increased from 50% in 1987 to 64% in 2001. In a large international European research depression detected at an average of 69% (45–94%) of patients with somatic diseases.

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Gastrointestinal (GI) disease is a serious illness, which frequently affects a patient's physical and emotional wellbeing as well as being heavily affected by stress. Meanwhile depression and anxiety have been identified as risk factors for some GI diseases.

Various studies using a variety of assessment methods have demonstrated that high levels of depression and anxiety exist in patients with GI symptoms. It has also been shown that patients with comorbid anxiety and depressive disorders tend towards more severe symptoms, longer recovery times, poorer outcomes, and greater use of healthcare resources. Despite the likelihood of GI patients to suffer from emotional distress, it has been reported that physicians in the GI department often fail to identify most cases of depression and/or anxiety, leading to under-treatment in 40%-90% of patients.

The medical literature often suggests that anxiety and depression are underdiagnosed and undertreated in the primary care setting, and that patient outcomes will inevitably improve if family physicians simply learn to better recognize and treat standard psychiatric syndromes with therapies derived from the psychiatric practice.

Family physicians understand that personality disorders, substance abuse and somatization disorders are common in the primary care setting and that anxiety often coexists. Moreover, family physicians are always balancing priorities, not just among coexisting and overlapping psychiatric syndromes, but between these and other acute and chronic disorders faced by patients. In primary care, the patient with Generalized Anxiety Disorder as the highest priority disorder is unusual if not rare. Previous studies have shown that depression and anxiety are risk factors for diseases of the digestive system. Digestive system disease patients with depressive and anxiety disorders often have more serious somatic symptoms, longer time to disease recovery and worse prognosis, and therefore tend to consume more medical resources. On the other hand, several studies have shown that the prevalence of depressive and anxiety disorders in patients with digestive system diseases is often high, and these patients tend to visit the gastroenterology department of general hospitals because of more prominent digestive system symptoms, mild depressive or anxiety symptoms, or the concern of being labelled as "mentally ill patients". Stanford study researchers have previously thought that stress hormones were the reason that people with digestive problems were more anxious and depressed. More recent studies, such as the one at Stanford, have implicated childhood Gastroenterological issues that occurred before the person's psychological symptoms developed.

A large body of research into complementary and alternative therapies has examined the relationship between the mind and the body, but the Stanford study focused on how the body can directly affect the mind. The evidence led the researchers to note that the condition of a person's stomach can directly affect the way they think and behave. The primary mechanism identified was a signal from the stomach to the brain that causes a permanent change. Scientists are further investigating precisely how that communication is triggered and sent to the brain. This could lead to new treatment therapies for anxiety and depression.

Based on research in this area, experts came to believe that anxiety and depression may sometimes be caused by electrical stimulation of the vagus nerve. This belief prompted the development of new therapies for treatment-resistant depression.

The prevalence of emotional disorders in Gastroenterological patients have been assessed in a number of studies throughout America, Europe, and China, including the Hong Kong and Taiwan regions. However, the economic status and cultural traditions of mainland China are unique, and likely to make the situation of mainland Chinese Gastroenterological patients distinctive.

Although digestive system diseases are closely related to anxiety, depressive and other mood disorders, studies have shown that the symptoms of mood disorders, such as depression and anxiety, in the vast majority of patients with digestive system diseases cannot be identified by gastroenterologists. As a result, 40–90% of patients with depressive and anxiety disorders cannot acquire corresponding medical and health services and treatment.

There are many methods for the determination of anxiety and depression in clinical practice: Hamilton Rating Scale for Anxiety and Depression, Back Anxiety and Depression Inventory, Zung Self-Rating Scale for Anxiety and Depression, Hospital Anxiety and Depression Scale (HADS), Social Phobia Inventory, Panic Disorder Severity Scale. But among them only HADS is designed to study anxiety and depression in somatic patients, which could be used not only by psychiatrists, clinical psychologists, but also by other specialists.

HADS was originally developed by Zigmond and Snaith (1983) and is commonly used by internal doctors to determine the levels of anxiety and depression that a patient is experiencing. The first review about using HADS in the internal medicine practice was published in 1997. "The HADS was found to perform well in assessing severity and caseness of anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary case patients and the general population". In addition to frequent validation for use in elderly HADS has been validated for use in adolescents.

Zigmond and Snaith created this outcome measure specifically to avoid reliance on aspect of these conditions that are also common somatic symptoms of illness, for example fatigue and insomnia or hypersomnia. This it was hoped would create a tool for the detection of anxiety and depression in people with physical health problems.

Patients and Methods

In our study we examined a group of patients with Gastroenterological diseases: Chronic Gastroduodenitis, Peptic Ulcer Disease, GERD, Chronic Enterocolitis, Dysbacteriosis, Chronic Cholecystitis, Chronic Pancreatitis to estimate the prevalence and detection rates of anxiety and depression. A study anxiety and depression in patients with Gastroenterological Diseases was conducted on the basis of Outpatients department of "Batumi Seamen's Medical Center 2010" n 116 patients with Gastroenterological Diseases, among them 70 female/46 male, aged 18–72.

For our studies was selected Hospital Anxiety and Depression Scale of which is especially used by Doctors of Family Medicine and Therapeutists in the conditions of Outpatient Department. Test details included: One questionnaire, comprising 14 questions; the questionnaire fea-

tures 7 questions for anxiety and depression of which can be answered within 2–5 minutes; individual assessment; suitable for administration by a range of clinical professionals along with researchers assessing emotional disorders in adults; available in over 60 languages. Even-numbered questions relate to depression and odd-numbered questions relate to anxiety. Each question has 4 possible responses. The two subscales, anxiety and depression have been found to be independent measures. In its current form the HADS is now divided into four ranges: normal (0–7), mild, subclinical (8–0), moderate (11–15) and severe (16–21). The validation study HADS proved that it is an acceptable, reliable and valid measure of psychological distress.

We use some questions which revealed have or not patient anxiety and depression. We meet 116 patients who have Gastroenterological Diseases. They fill in the questionnaire. These questions gave us an opportunity to understand when the patient has anxiety, depression or both of them. We divided patients into two groups (male/female). Also we divided volunteers in three groups by age: 1 group: 18–30; 2 group: 31–50; 3 group: 51–72 years;

Discussion

In the present study we assessed anxiety and depression symptoms in patients with gastroenterological diseases by the HADS. Our results generally confirm the findings of other studies that there are high rates of psychological problems in patients of gastroenterological diseases and a lot of reasons could account for this. The study was conducted in the outpatient department. After the examination by the physician, the researches (116 patients) conducted an interview. During that interview "Anxiety" and "depression" was assessed according to the questions. Each item had been answered by the patient on a four point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety and depression. Two subscales, anxiety and depression, were independent measures. Subsequent experience enabled a division of each mood state info four rages: normal, mild (subclinical), moderate and severe and it is in this form that the HADS is now issued. In the case of illiteracy, or poor vision, the wording of the items and possible responses may be read to the respondent

Table 1

Index of prevalence of anxiety in patients with gastroenterological diseases

Disease	*Amount of Patients*			*Norm (0-7 sc.), %*	*Depression*			*Total*	
	Total	*F.*	*M.*		*Subclinical (8-10 sc), %*	*Moderate (11-15 sc.), %*	*Severe (16-21 sc.), %*	*Amount*	*%*
Chronic Gastroduodenitis	22	16	6	11–50	4–18.2	4–18.2	3–13.6	11	50
Peptic Ulcer Disease	12	7	5	2–16.7	3–25	4–33.3	3–25	10	83.33
GERD	24	16	8	11–45.8	5–20.8	4–16.7	4–16.7	13	54.16
Chronic Enterocolitis	28	15	13	14–50	6–21.4	3–10.7	5–17.9	14	50
Dysbacteriosis	9	4	5	1–11.1	1–11.1	3–33.3	4–44.5	8	88.8
Chronic Cholecystitis	11	6	5	3–27.3	3–27.3	3–27.3	2–18.1	8	72.72
Chronic Pancreatitis	10	6	4	2–20	4–40	3–30	1–10	8	80
Total	116	70	46	44–38	26–22.4	24–20.7	22–19	72	64.86

Table 2

Index of prevalence of depression in patients with gastroenterological diseases

Disease	*Amount of Patients*			*Norm (0-7 sc.), %*	*Depression*			*Total*	
	Total	*F.*	*M.*		*Subclinical (8-10 sc), %*	*Moderate (11-15 sc.), %*	*Severe (16-21 sc.), %*	*Amount*	*%*
Chronic Gastroduodenitis	22	16	6	14–63.7	3–13.64	3–13.64	2–9	10	45.5
Peptic Ulcer Disease	12	7	5	6–50	3–25	2–16.7	1–8.3	6	50.0
GERD	11	6	5	6–54.5	3–27.3	2–18.2	–	5	45.5
Chronic Enterocolitis	28	15	13	17–60.7	4–14.3	4–14.3	3–10.7	11	39.3
Dysbacteriosis	9	4	5	5–55.6	1–11.1	2–22.2	1–11.1	4	44.4
Chronic Cholecystitis	24	16	8	16–66.7	4–16.7	2–8.3	2–8.3	8	33.3
Chronic Pancreatitis	10	6	4	6–60	2–20	1–10	1–10	4	40.0
Total	116	70	46	70–60.3	20–17.2	16–13.8	10–8.6	48	41.38

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Table 3

Index of prevalence of anxiety and depression in patients with gastroenterological diseases

Disease	*Amount of Patients*	*Anxiety and Depression*	*%*
Chronic Gastroduodenitis	22	6	27%
Peptic Ulcer Disease	12	3	25%
GERD	11	2	18.2%
Chronic Enterocolitis	28	4	14.3%
Dysbacteriosis	10	2	20%
Chronic Cholecystitis	24	6	25%
Chronic Pancreatitis	9	4	44.4%
Total	116	27	23.27%

Our study showed that respondents of patients with gastroenterological diseases anxiety was noted in 64.86% (Table 1), depression – in 41.38% (Table 2), both anxiety and depression – in 23.27% of patients (Table 3). According to our research among the patients with anxiety, subclinical anxiety was noted in 22.4%, moderate-in 20.7%, and severe-in 19% of patients (Table 1). Among them high levels of anxiety was shown in patients with dysbacteriosis – 88.8%, peptic ulcer disease – 83.3%, chronic pancreatitis – 80%.

As for the depression, subclinical depression was observed in 17.2%, moderate depression-in 13.8%, and severe depression-in 8.6% of patients. (tab.2). Among them high levels of depression was shown in patients with Peptic Ulcer Disease – 50%, Chronic gastroduodenitis and GERD – 45.5%, both anxiety and depression dates is 23.27%. It should be noted that severe anxiety and depression especially were noted in man (63%), and depression was different in various ages – 38% (18–30 years), 37% (31–50years) and 25% (51–72 years).

Conclusion

The current adjusted prevalence of depressive disorders in our study was 41.38%. However, this value was 19.5% in a meta-analysis of primary care patients in ten countries.

The current adjusted prevalence of anxiety disorders reported in our study was 64.86%, which was higher than the 19.0% prevalence reported among Belgian outpatients in 86 general practices and the 19.5% prevalence reported in 15 United States general medical care centers. Both anxiety and depression in our study was 23.27%. However, the economic status and cultural traditions of Georgia are quite distinctive from foreign countries

Although digestive system diseases are closely related to anxiety, depressive and other mood disorders, studies have shown that the symptoms of mood disorders, such as depression and anxiety, in the vast majority of patients with digestive system diseases cannot be identified by gastroenterologists. As a result, 40–90% of patients with depressive and anxiety disorders cannot acquire corresponding medical and health services and treatment

Most general physicians are not appropriately trained in psychiatry and cannot diagnose or treat depressive and anxiety disorders. Thus, Gastroenterological disorders physicians tend towards a low detection rate. It is meaningful to investigate overall prevalence of depressive and/or anxiety disorders in Gastroenterological outpatients to understand the actual patient population involved and the importance of diagnosing such disorders. The Family Medicine Doctors are in a unique position to recognize psychiatric morbidity and to take appropriate measures.

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Meeting Calendar

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October 19–23, 2019 Beijing, China

17 INTERNATIONAL CONGRESS ON IMMUNOLOGY

♦

December 12–14, 2019 Lyon, France

WORLD ALLERGY CONGRESS

♦

July 2–5, 2020 Saint Petersburg, Russia

XIII WORLD *ASTHMA, ALLERGY & COPD* FORUM

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CANCER CHECKPOINT BLOCKADE

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In 2018б Drs James Allison and Tasuku Honjo received the Nobel Prize in Physiology and Medicine for their research in cancer therapy by activating the immune response. The discovery of regulatory molecules that are responsible for preventing the hyperactivation of T-lymphocytes and their programmed death has initiated the innovative method of targeted immunotherapy called *immune checkpoint blockade* (ICPB). ICPB is used to block a tumor's control systems and restore the anticancer immune response. CTLA4 (cytotoxic T-lymphocytic antigen 4) was the first target which blockade has led to increasing of antitumor immunity. The second targets were the receptor PD-1(programmed death 1) and its ligand PD-L1. Tumors expressing PD-L1 can convert cytotoxic lymphocytes into inactivated ones through the interaction of the inhibitory receptor PD-1. In addition, the determination of tumor expression PD-L1 allows select patients for making the timely treatment. The success of PD-1 and PD-L1 inhibitors points out the versatility of immunotherapy as a cancer-treating modality. Such immune checkpoint blockers include anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab and nivolumab) and anti-PD-L1 (avelumab, atezolizumab), which have proved to be highly effective against a number of malignancies. Durvalumab and avelumab (antiPD-L1 inhibitors) have also been approved for clinical use. In clinical trials these drugs have shown good results and have become the standard therapeutic option for a few types of malignant tumors. In addition, it was found that PD-1 and CTLA-4 pathways have an irregular role in inhibiting the immune response to cancer growth, and therefore, are used in combination therapy of ICPB. Thus, a combination of nivolumab and ipilimumab has proved to be more effective in patients with metastatic melanoma than monotherapy. In 2016 combination therapy with these two drugs was approved for using in inoperable or metastatic melanoma. A combination of standard chemotherapy (CT) and ipilimumab are used to enhance the effect of antitumor therapy in modern oncology, that leads to increasing the activity of $CD4^+$-and $CD8^+$-T-cells, as well as the production of proinflammatory cytokines (IL2, IL12) and GM-CSF. Pembrolizumab has been approved for using in first- and second-line treatment of metastatic urothelial cancer (UC), whereas nivolumab is recommended as a second-line therapy after platinum-based CT regimens have been exhausted. Thus, fundamental research in the field of immunology, as well as the interdisciplinary approach in oncology opens up the new opportunities and prospects in the diagnosis and treatment of diseases that previously have been considered incurable. *The publication has been prepared with the support of the «RUDN University Program 5-100».*

FEATURES OF THE IMMUNE RESPONSE TO CO-INFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS C VIRUS

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Recently, it became known that coinfection with viruses that cause chronic infections with damage to the immune system, leads not only to significant changes in the mechanisms of the immune response, but also shows dependence on the order of the pathogens infections. At the same time, the immune response due to the participation of dendritic cells, T-helpers and cytotoxic T-lymphocytes is much more pronounced on the first pathogen than on the virus coming later. For this reason, the infectious process caused by the later virus is much more severe, accompanied by a marked drop in the rate of elimination of the pathogen from the patient's body, adversely affects the results of the antiviral therapy. On the example of HIV and HCV coinfection, we have shown that in cases when HIV enters the host earlier than HCV, chronic hepatitis C proceeds with a higher frequency of progressive liver fibrosis (about 1.5 times) against the background of a higher viral load of HCV. It turned out that it is important not only the order of receipt of pathogens, but also the period of time that separates the infection of the host with these two pathogens. The most favorable prognosis for the development of chronic hepatitis C occurs in two cases – when HIV enters the host first, with the time between the arrival of two pathogens is 5 years or more. A similar situation for a more favorable course of liver fibrosis in patients with chronic hepatitis C can be observed when the first pathogen is HCV in HIV coinfection over the next 5 years. In all these cases, there is a higher blood content of $CD3^+CD8^+$ cytotoxic T-lymphocytes, which determines a more favorable course for HIV infection. Thus, the conditions of entry of such viral pathogens with immunosuppressive effects as HIV and HCV into the human body during coinfection are decisive factors determining the course of the infectious process. *The publication has been prepared with the support of the «RUDN University Program 5-100».*

SEASONAL EXACERBATION OF ASTHMA IS FREQUENTLY ASSOCIATED WITH RECURRENT EPISODES OF ACUTE URTICARIAL

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Background: Asthma and urticaria are both mediated in part, by increased release of histamine from highly activated mast cells. However, they are pathophysiologicaly different as mast cell degranulation in these two disorders is of different mechanisms. ***Objective:*** To assess the incidence of urticaria in patients with asthma, and of asthma in patients with chronic spontaneous urticaria (CSU). Patients and Methods: Asthma patients (n=110) with intermittent (seasonal exacerbation) or

International Journal on Immunorehabilitation
2019 Volume 21 No 1

chronic disease as well as healthy control subjects (n=100), were assessed for the incidence and character of urticaria and followed over the course of one year to check if episodes of urticaria are linked to changes in asthma activity. Also, we prospectively assessed CSU patients (n=95) for the incidence of asthma for one year. ***Results***: Episodes of urticaria occured in 26 of 110 asthma patients (23.6%), but only 2 of 100 healthy control subjects (2%) ($p<0.0001$). During the one year observation period, episodes of urticaria were significantly more frequent in asthma patients with positive skin prick test reactions (mainly to grasses, Parietaria Judaica and trees), and occurred mostly during seasonal asthma exacerbation, i.e. acute episodes of urticaria. The incidence of asthma in CSU patients was 10.5% (10 of 95 patients), and similar to that in the general healthy control population. ***Discussion:*** Our prospective study demonstrates, for the first time, that asthma patients frequently develop acute urticaria, mainly during seasonal exacerbations. In contrast, CSU patients do not show increased incidence of asthma.

BRONCHODILATION TESTS WITH IPRATROPIUM-BROMIDE VS SALBUTAMOL IN ASTHMATIC ADULTS: DIFFERENCES IN RESPONSE TO COLD AS A TRIGGER OF ASTHMA SYMPTOMS

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A heterogeneous response to beta-agonists and muscarinic-antagonists is reported in asthmatics. We evaluated separately the bronchodilation after ipratropium bromide (IB) and after salbutamol and searched for possible predictive factors of positive response to these bronchodilators. ***Methods***: 53 asthmatics consecutively referred for investigation to our Allergy Department were studied. Age range was 18–75 years, with asthma severity mild to moderate. Patients underwent history taking, physical examination, skin prick tests (SPTs), total IgE determination, CBC, 24-hour Holter ECG monitoring (ECG-Holter), spirometry and bronchodilation test (BDT) with IB and salbutamol separately. We have looked for possible association between the response to Ipratropium Bromide and Salbutamol and the different factors triggering asthma symptoms as reported by the patient in a questionnaire on the history of the disease. ***Results***: 41 patients showed a positive BDT: 11 only to IB, 8 only to salbutamol, 22 to both drugs. We found that the subgroup responding to IB only showed a significant higher prevalence of patients reporting exposure to cold as a trigger of asthma symptoms with respect to the subgroup responding to Salbutamol only. Cold was reported as a trigger of asthma in the subgroup of IB responders in 8 out of 11 patients, while in the subgroup of Salbutamol responders only 2 out of 8 patients ($p=0.040$). ***Conclusions***: To our knowledge this is the first study showing that triggering by cold of asthma symptoms characterize patients electively responding to a muscarinic antagonist agent.

THE ROLE OF IRON-RESPONSIVE ELEMENT-BINDING PROTEIN 2 (IRP2) IN RESISTIVE BREATHING-INDUCED PULMONARY INFLAMMATION

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Rationale: Iron metabolism is implicated in the pathogenesis of obstructive airway diseases, such as asthma and COPD. IRP2 is a key mediator of iron metabolism. We have previously shown that resistive breathing (RB), such as that encountered in asthma and COPD exacerbations, induces pulmonary inflammation. We investigated the role of IRP2 in RB-induced pulmonary inflammation. ***Methods:*** Adult male IRP2 knockout (IRP2-/-) and C57BL/6 wild type mice were subjected to RB by tracheal banding. Briefly, anesthetized mice were placed under a surgical microscope and a nylon band was sutured around the trachea to provoke a 50% reduction of surface area. Following 24 hours, the mechanical parameters of the respiratory system were measured and bronchoalveolar lavage (BAL) was performed to measure total and differential cell count. IL-1b and IL-6 were measured in BAL fluid. ***Results:*** RB increased tissue elasticity in wild type mice ($p=0.008$ to ctr). In contrast, in IRP2-/- mice tissue elasticity did not change ($p=0.02$ to wild type). RB increased BAL cellularity ($p=0.001$ to ctr), due to raising macrophage count ($p=0.002$ to ctr). In IRP2-/- mice, no increase in total BAL cell and macrophage count was observed ($p<0.001$ to wild type). IL-1b and IL-6 were upregulated following RB ($p=0.01$ and $p=0.003$ to ctr, respectively). No increase in the IL-1b and IL-6 levels was observed in IRP2-/- mice ($p=0.003$ and $p=0.04$ to wild type, respectively). Conclusions: IRP2 has an important role in the pathogenesis of pulmonary inflammation following resistive breathing, in an experimental model of severe airway obstruction.

CRITERIA FOR THE DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY AT THE LEVEL OF FAMILY DOCTORS CENTER

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Immunodeficiency diseases have a significant impact on morbidity and mortality rates of the population due to the chronic relapsing course and resistance to therapy. In Moldova, there is no National Register of primary immunodeficiencies

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(PID) and the latter appear under the "mask" of various nosological forms. The purpose of this work was to develop basic criteria for the diagnosis of primary immunodeficiencies at the level of the Center for Family Doctors. Six hundred and seventy cards of complex medical examinations of patients with suspected PID were analyzed using clinical, instrumental, laboratory tests (complete blood count, immunogram with determination of population content and lymphocyte subpopulations, serum immunoglobulin classes M, G, A, E-total) and others. Based on the multivariate analysis, the most informative basic criteria for identifying PID at the primary health care level were selected, which included risk factors, nosological forms proposed by WHO, a history of the disease, data of an objective examination of the patient and laboratory test results. PID was characterized depending on age (in newborns and babies aged 5–6 months, in children aged 6 months –5 years, in children aged 5 and adults). There were identified 21 cases of PID of which 11 were confirmed by molecular genetic methods. Thus, the use of these criteria will contribute to the early detection of patients with suspected PID, and a comprehensive clinical, immunological, and molecular genetic examination confirms the diagnosis at the tertiary level of medical care.

THE EFFECTS OF PHARMACOLOGICAL INHIBITION OF PRO-INFLAMMATORY CYTOKINES IN THE PATHOGENESIS OF EXPERIMENTAL OF HDM-INDUCED ASTHMA MODEL IN MICE

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Patients with a complicated form of asthma, who have both eosinophilic and neutrophilic infiltration in the lungs are often poorly treated with standard treatment methods, including the use of corticosteroids. Thereby, more effective treatment is anti-cytokine therapy, accepted to inhibit the effects of pro-inflammatory cytokines. The targeting of anti-IL-4/IL-5 and anti-IgE therapeutic antibodies, was approved for severe asthma treatment, but was only effective in relation to eosinophilic type and does not affect neutrophilic asthma. TNF and IL-6 are the key mediators of inflammation that play an important role in the pathogenesis of asthma [1]. However, patients with systemic anti-TNF therapy demonstrate side effects [2]. We hypothesize that the combined inhibition of several cytokines may be more safe and effective for patients with mixed asthma. The aim of this work was to address the efficacy of IL-6 and TNF pharmacological inhibition in the experimental mouse model of severe mixed asthma induced by the house dust mite (HDM) extract. The simultaneous administration of TNF and IL-6 inhibitors with each intranasal immunization of HMD showed the reduction of the number of granulocytes and the production of IgE in bronchoalveolar fluid compared with individual inhibition of these cytokines. In addition, the combined anti-cytokine therapy prevented the overexpression of Th17-associated cytokines and the recruitment of pathogenic Th17 cells in the lungs caused by anti-TNF monotherapy. Thus, the obtained results confirm our hypothesis about the significant efficacy of combined pharmacological inhibition of TNF и IL-6 in neutrophilic-eosinophilic asthma, compared with individual inhibition of these cytokines. *The work was supported by the Russian Science Foundation grant 19-75-30032*

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METABOLIC CHARACTERISTICS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASTHMA

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The present study evaluated the profile of metabolic abnormalities in asthma and chronic obstructive pulmonary disease (COPD) patients. This was a cross sectional case controlled study of 40 patients with COPD, 40 patients with asthma and 40 controls. The following were assessed: anthropometric indices, blood pressure, serum lipid profile, fasting blood sugar and spirometric evaluation. We analyzed the differences in metabolic score between these three groups and also the correlation between these scores and patient characteristics. The prevalence of MetS was 57.5%, 40%, and 30% in the asthma, COPD and control group respectively. For the asthma group, low high density lipoprotein (HDL) and abdominal obesity were the commonest metabolic abnormality. For the COPD group, low HDL cholesterol was the commonest metabolic abnormality. Impaired fasting glycaemia followed by abdominal obesity were the commonest metabolic abnormalities in the control group. Waist circumference, fasting blood sugar (FBS), triglyceride, albumin and diabetes mellitus (DM) correlated significantly with asthma ($p<0.05$). While body mass index (BMI), triglyceride, HDL-Chol, DM and hypertension (HTN) correlated significantly with COPD ($p<0.05$). In multivariate analysis, among the components of MetS, FBS, DM and diastolic blood pressure (DBP) are significantly associated with asthma. While DM, DBP, BMI and triglycerides are significantly associated with COPD. Thus, the prevalence of the Mets in persons with asthma appears to be high. Secondly, there is a high prevalence of lipid abnormalities and obesity in all the study groups. Thus, screening for components of metabolic syndrome could form a part of routine work-up of these patients.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

CROSS-REACTIVE CARBOHYDRATE DETERMINANT (CCD) INHIBITION TEST CAN HELP TO IDENTIFY FALSE POSITIVE FOR PLANT ALLERGEN SIGE CAUSED BY CCD

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Background: Pollen allergens are important inhaled allergens and can cause respiratory allergic diseases, especially seasonal allergic rhinitis and asthma. The pollen specific IgE (sIgE) tests are often affected by cross-reactive carbohydrate determinant (CCD), cause false-positive reactions. This study analyzed the sensitization of pollen allergens in south China and discussed the effect of CCD inhibitor on the results of sIgE test of pollen allergen and seed food allergen. ***Methods:*** Two hundred and thirteen patients, with a doctor's diagnosis of allergic rhinitis or asthma, IgE towards at least two common inhaled allergens were recruited. Serum samples were analyzed for sIgE against tree mix (willow/poplar/elm Tree), common ragweed, mugwort, humulus scandens, peanut, soy, and cross-reactive carbohydrate determinants (CCD) and specific IgE-binding inhibition experiments were performed. ***Results:*** Among the patients sensitized to multiple allergens, 83 patients (39.0%) were plant allergen sensitization (sIgE positive for any of the above six allergens was defined as plant allergen sensitization, PAS), and 57.8% of PAS patients were positive to CCD-sIgE. PAS subjects were more often sensitized to CCD, known to be cross-reactive between grass and seeds. CCD inhibited binding to pollen and seed allergen by 73.0% to 100.0% The highest inhibition rate was obtained for Humulus scandens (100.0%), followed by mugwort and peanut (both 85.2%), common ragweed (81.5%), soy (80.0%) and tree mix (73.0%). It was surprised to find that all sIgE against to pollen and seeds from 23 PAS patients were turned to negative after CCD inhibition. Conclusion More than 73% plant allergens-sIgE were eliminated into negative after CCD inhibition experiment, suggesting the majority plant allergen-sIgE in southern China, particularly the sIgE against peanut, soybean and pollen allergens, were false-positive caused by the CCD interference. CCD inhibition test should be used in clinical diagnosis, which can help to avoid misdiagnosis of plant allergens allergy.

STUDY OF FUNGAL ALLERGEN AND ASPERGILLUS FUMIGATUS COMPONENT SENSITIZATION IN A SOUTHERN CHINESE COHORT

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Background: Fungal spores and hyphal fragments in air reportedly caused immunoglobulin E (IgE)-mediated respiratory allergic diseases. Here, we analysed the prevalence of fungal allergens in patients in Southern China. We analysed the roles of Aspergillus components in the differential diagnosis of ABPA and asthma. ***Methods:*** A total of 4033 patients with respiratory diseases were enrolled to analyze the prevalence of Aspergillus fumigatus; 195 adult patients were further examined for sIgE against Aspergillus fumigatus, *Penicillium chrysogenum*, *Cladosporium herbarum*, *Mucor racemosus*, *Candida albicans*, *Alternaria alternata* and Helminthosporium halodes; and 18 allergic bronchopulmonary aspergillosis (ABPA) and 54 asthmatic patients were tested for sIgE against Aspergillus fumigatus components. Results: Two hundred and ninety-five (7.30%) patients were sIgE-positive for *Aspergillus fumigatus*, with a median sIgE level of 1.10 kU/L. The positive proportion and median level of sIgE against *Aspergillus fumigatus* were higher in adults than in children. In total, 666 fungal allergen sIgE-positive samples were found in patients who were tested seven fungal allergens. Aspergillus fumigatus was the most common, accounting for 21.8%, followed by Candida albicans (18.6%, 124/666), *Penicillium chrysogenum* (18.0%), *Helminthosporium halodes* (12.5%). The positive rates of sIgE against six fungal allergens in patients who were sensitized to Aspergillus fumigatus ranged from 37.9% to 77.9%, most of which were observed in *Penicillium chrysogenum* (77.9%). Aspergillus fumigatus was correlated well with all other fungi. The correlation between Aspergillus fumigatus and Asp f 2 was the strongest. The positivity rate and sIgE level of Asp f 1, Asp f 2 and Asp f 6 were significantly higher in patients with ABPA than in patients with asthma ($p<0.05$). ***Conclusion***: In southern China, patients with respiratory tract allergic diseases are often sensitized to multiple fungal allergens possibly due to the cross-reaction between fungal allergens. Detection of Aspergillus fumigatus components may be helpful for diagnosing ABPA and asthma.

ASSOCIATION BETWEEN COW'S MILK PROTEIN HYPERSENSITIZATION AND VITAMIN D INSUFFICIENCY IN CHILDREN SUSPECTED OF COW'S MILK PROTEIN ALLERGY

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Background: Vitamin D insufficiency has been associated with immune dysfunction and linked to atopic diseases. It may increase the risk of cow's milk protein sensitization. ***Objective***: This study aimed to determine the association between vitamin D insufficiency and cow's milk protein sensitization among children suspected of cow's milk protein allergy (CMPA). ***Methods:*** Seventy children suspected of CMPA, aged less than 5 years, were recruited from Thammasat Universi-

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ty hospital. Their serum was measured for specific IgE levels to cow's milk protein by immunocap method and 25-hydroxyvitamin D (25OHD) concentration by enzyme-linked immunosorbent assay. Vitamin D insufficiency was defined by the serum 25OHD levels of <30 ng/ml. Sensitization was defined by serum specific IgE level of >0.35 kUA/L. ***Results:*** There were 45 boys (64.3%) with the mean age of 16.4 months (SD=11.5 months). Exclusive breast feeding during the first 4 months was documented in 24 children (34.2%). The most frequent clinical manifestations were of the immediate type (61.4%) including history of angioedema, urticaria and wheezing. The prevalence of vitamin D insufficiency and sensitization to cow's milk protein was 24.3.0% (95% CI: 14.6–36.0%) and 42.9% (95% CI: 31.1–55.3%) respectively. Children with sensitization to cow's milk protein had higher risk of vitamin D insufficiency with the risk ratio of 1.6 (95% confidence interval: 0.9–2.6) ***Conclusions***: Vitamin D insufficiency is prevalent in children suspected of CMPA. Lower vitamin D levels were found in children with sensitization to cow's milk protein.

A RANDOMIZED, DOUBLE-BLIND, PHASE III NON-INFERIORITY CLINICAL TRIAL TO ASSESS EFFICACY AND SAFETY OF TRIAMCINOLONE ACETONIDE NASAL SPRAY IN COMPARISON WITH FLUTICASONE PROPIONATE NASAL SPRAY IN ADULTS SUFFERING FROM PAR (PERENNIAL ALLERGIC RHINITIS) IN RUSSIA

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Background: Allergic rhinitis (AR) affects ~24% of the population in Russia. Intranasal steroids are the most effective drug class for managing AR symptoms. Triamcinolone acetonide is a glucocorticoid presented on the OTC markets in different countries, but not in Russia. The purpose of this study was to demonstrate non-inferior efficacy of triamcinolone nasal spray in Russian adult population, suffering from perennial AR (PAR), versus a reference product, fluticasone propionate, which is the only nasal corticosteroid with OTC status in Russia. ***Methods:*** A randomized, double-blind, parallel-group, multicentre, phase III non-inferiority clinical trial was conducted (NCT 03317015) and sponsored by Sanofi. Patients with PAR were treated either with triamcinolone nasal spray (55 µg per spray, 2 sprays per nostril once a day) or with fluticasone nasal spray (50 µg per spray, 2 sprays per nostril, once a day) for 28 days. The primary aim was to assess efficacy of triamcinolone vs fluticasone by rTNSS (reflective total nasal symptom score) after 28-days treatment compared with baseline. A non-inferiority margin of 10% was used. ***Results:*** 260 patients were randomized, 257 completed the study and 256 (128 *vs.* 128) were included in the per-protocol set. Change of rTNSS (24 h) from baseline (0 day) to the last day of treatment was – 8.2 3.00 in the triamcinolone group and – 8.0 2.80 in the fluticasone group. There was no significant difference between the groups in rTNSS changes from baseline to the end of treatment (p=0.457). For confirmation of non-inferiority (for negative version of rTNSS change from baseline), the upper limit of one-sided 97.5% CI for difference in treatment groups should be less than +0.8 (+10%), which equals to the upper limit of two-sided 95% CI. Mean difference between groups for change from baseline is 0.172 (95% CI -0.886 to 0.543) calculated by t-test, the upper confidence limit is 0.543, and it is lower than the stated non-inferiority margin (0.8), supporting the conclusion that efficacy of triamcinolone measured by changes of rTNSS is non-inferior to efficacy of fluticasone. Triamcinolone acetonide nasal spray was well-tolerated in patients with PAR (18 AEs in 13 patients in triamcinolone and 21 AEs in 12 patients in fluticasone group).

EPIDEMIOLOGY OF ALLERGIC RHINITIS IN POPULATION OF SCHOOL AGE CHILDREN – REGION OF ADJARA

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Allergies' morbidity share of allergic rhinitis is quite high. Its prevalence in children's population varies within 15–25% (ARIA). Symptoms of AR can potentially impair patients' ability to sleep and perform optimally in their daily professional or personal life. Children's education is also particularly affected. All the above determined the goal of our work. ***Goal***: The purpose of this study was to assess the prevalence of AR in the school children population in Ajara, with emphasis on descriptive parameters in 6 distinct geographical regions. ***Methods:*** For the first stage of study we developed the questionnaire. Studied population included 738 children. Screening was conducted by means of the initial questionnaire oriented towards first diagnostics of allergic rhinitis. Second stage included clinical-allergic study: prick-test in vivo (included food, plants, epidermal and domestic allergens). ***Results:*** On the basis of self-reporting, 21.8% (161 persons) of the study population was considered to have AR. From symptoms of allergic rhinitis 57.7% of the studied population had sneezing, 31.6% – rhinorrhea, 49% – nasal obstruction, 36% – nasal itch and the mentioned symptoms (respondents could choose more than one answer). Respondents with AR symptoms (97 persons – 60%) indicated seasonal nature of the disease. At the second stage, In the results of *in vivo* study of the allergens there prevailed sensitization caused by domestic dust – 65.2% of cases and in 25% of cases it was caused by epidermal allergens of the cats and dogs and in 9.8% - plant allergens (there were used prick-tests). Conclusion Epidemiological study of allergic rhinitis in children's population of Batumi, Adjara, showed that AR prevalence was 21.8%. Prevalence of symptoms was reliably higher in the urban areas, than rural.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

THE IMPACT OF ATOPIC SENSITIZATION ON RECURRENT LARYNGOTRACHEITIS IN CHILDREN

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Generalization of results of an allergological examination of children with recurrent laringotracheitis (RLT), monitoring during three years and researching of an association between RLT and atopic sensitization. ***Methods***: Eighty children (52 boys and 28 girls) 3–15 years old with RLT were investigated (64 children 3–7 years old and 16 children 7,1–15 years old). Allergodiagnostic included: patch-tests, total serum and specific IgE. ***Results:*** More than a half (47/58.75%) of investigated children with RLT had allergic deseases: seasonal allergic rhinitis, allergic rhinitis, atopic dermatitis, bronchial asthma. Essentially a half of relatives of mother's or on father's side of the family had allergic deseases. IgE levels varied from 50 to 2000 IU/ml, a polysensitization was noted (household, pollen allergens). Sensitization wasn't identified in 33 (41.25%) children. Seasonal allergic rhinitis was diagnosed in 20 (25%) children, atopic dermatitis – in 21 (26.2%), allergic rhinitis – in 6 (7.5%), the combination of seasonal allergic rhinitis and atopic dermatitis – in 6 (7.5%), bronchial asthma – in 20 (25%). ***Conclusion:*** Manifestations of allergic deseases were diagnosed in more than a half of children (58.75%) with RLT. The predisposing factor is a hereditary load in atopic diseases: a part of relatives (48.5%) of mother's or on father's side had allergic diseases. A three-year case-monitoring showed than a quarter of children (20–25%) had bronchial asthma. Children with RLT and hereditary load in atopic diseases need for an allergologist medical supervision.

A NEUTROPHIL HYPERSENSITIVITY SYNDROME TO TOXICANTS AS A BASIS OF PATHOGENESIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Objective: The aim of the study was to investigate hypersensitivity to toxicants (tobacco and exhaust gases of diesel internal-combustion engines) by evaluating the myeloperoxidase (MPO) release from neutrophils in patients with chronic obstructive pulmonary disease (COPD). ***Methods***: The patients with moderate and severe COPD (GOLD) (n=26) were included in the study. The control group consisted of healthy volunteers with normal lung function (n=22). The groups had no difference in sex, age, smoking index, body mass index. We used cigarette tobacco extract (CTE), cigarette smoke extract (CSE) and solution of exhaust gases of diesel internal-combustion engine (EGS) as allergens. Dynamics of the MPO levels in saliva and cell-free supernatant was measured after exposed to toxicants (CTE, CSE, EG). ***Results:*** There were statistically significant differences in the groups after leukosuspension exposed to CTE. The MPO levels increased in the patients with COPD by 99% ($p<0.001$). The MPO levels increased in healthy volunteers by 60%. CSE did not cause degranulation of leucocytes and it did not release the MPO in cell-free supernatant in control group. There was an increase in the MPO levels by 24% ($p<0.001$) in patients with COPD. An increase of the MPO levels were about 30% after leukosuspension exposed to EGS in patients with COPD, which exceeded the control group ($p=0.046$). Positive reactions were observed significantly more often in the saliva after CTE exposure in the COPD group as compared to the control group ($p<0.05$). A hypersensitivity of neutrophils of oral cavity to CTE was detected in 40% of smokers ($p<0.05$) in the control group. ***Conclusions:*** A neutrophil hypersensitivity syndrome to toxicants was detected by evaluating the MPO release from neutrophils in patients with COPD. Neutrophils of patients with COPD reacted to toxicants significantly more often and more strongly than healthy volunteers' neutrophils. The initial genetically determined hypersensitivity of neutrophils in patients with COPD to smoke and other inhalation toxicants leads to their degranulation and release of mediators and enzymes. It is a driving factor of inflammation in the airways.

PECULIARITIES OF APOPTOSIS, EXTRACTIONS MEMBRANE DISAGGREGATED MICROPARTICLES AND CYTOKINE IN DAMAGE TO LYMPHOCYTES IN PEOPLE OF YOUNG AGE IN COMBINING BRONCHIAL ASTHMA AND OBESITY

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Bronchial asthma is one of the most common respiratory diseases, in which many cellular elements are involved. It is interesting to study the peculiarities of bronchial asthma, changes in cellular and cytokine profiles in young patients with obesity. The purpose of the study was to identify the features of apoptosis and the peculiarities of membrane disaggregated microparticles in lymphocyte damage in patients young age with bronchial asthma, depending on the body mass index (BMI). 224 people were examined. The subjects were divided into 4 groups: group 1 – bronchial asthma and BMI 18.5–24.9 kg/m^2, group 2 – bronchial asthma and BMI 30–34.9 kg/m^2, group 3 – control, BMI 18.5–24.9 kg/m^2 and group 4 – control, BMI of 30–34.9 kg/m^2. All patients underwent a clinical and functional examination; blood sampling was performed to determine adipokines, cytokines, and lymphocyte secretion. The number of apoptotic cells was evaluated by the TUNEL method. Microscopy was carried out with the Olympus CX41 microscope, FITC-positive cells were noted, and the number of membrane disaggregated microparticles was counted. Statistical processing was performed in the program Statistica 10. When studying the content of adipokines in the blood, an increase in the level of leptin with a simultaneous decrease in the level of adiponectin in patients with obesity with a bronchial asthma compared with patients with normal weight was shown. There

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was an increase in plasma TNF-α, IL-6, IL-4, as well as a decrease in IL-15 in patients of the 2nd group compared to group 1 and control. It was found that in patients with bronchial asthma, in combination with obesity, the percentage of cells in apoptosis was significantly lower, in comparison with the control group with obesity, similar changes were noted in patients with bronchial asthma and normal body weight. Also in group 2 patients, the number of membrane disaggregated microparticles significantly increased in comparison with group 4, whereas in group 1 patients, on the contrary, significantly decreased in comparison with group 3. In patients with a combination of bronchial asthma and obesity, there was a negative correlation between IL-4 and adiponectin, as well as a direct relationship between the number of membrane disaggregated microparticles and FEV_1. Thus, it can be assumed that imbalance of cytokines, adipokines and mechanisms of programmed cell death is an important pathogenetic factor in both bronchial asthma and in the case of bronchial asthma and obesity.

EXPERIMENTAL APPROACHES TO IMPROVE THE IMMUNOSUPPRESSIVE FUNCTION OF MULTIPOTENT MESENCHYMAL STROMAL CELLS *IN VITRO*

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Due to the immunosuppressive properties the multipotent mesenchymal stromal cells (MSCs) are considered as a promising tool for the treatment of autoimmune and chronic inflammatory diseases. The outcome of MSC interaction with immune cells was shown to depend on a number of factors that can be regulated in vitro to alter the rate of immunosuppression that appears to be a promising direction in cellular technology development. The enhancement of MSC immunosuppression is currently known to be governed by the duration of interaction, MSCs/lymphocytes ratio, direct cell-to-cell contact, the use of early passaged MSCs, and pro-inflammatory induction (Krampera M. et al., 2006, McIntosh K. et al., 2006, Lin C.S. et al., 2012 Kim et al., 2014). We attempted to identify the factors and approaches to modify MSCs that can be used to enhance the immunomodulatory activity. The suspended MSCs were found to have averagely two times more pronounced antiproliferative effect on PHA-activated lymphocytes compared to adhered ones. Such a microenvironmental factor as O_2 level significantly modulated the properties of human adipose tissue-derived MSCs: at low O_2 (5%) the antiproliferative effect of MSCs was enhanced, and the cytokine profile was shifted towards the anti-inflammatory. At the same time, the expression of genes involved in immune response suppression (FOXP3, IL10, TGFB, PDCD1, etc.) was upregulated in lymphocytes, and the level of immunomodulatory molecules such as galectin 1, 3, and TLR4 on MSC surface increased as well. In addition, we observed the cytotoxic effects of lymphocytes on MSCs with relatively high intracellular ROS that can affect the immunosuppression effectiveness. Thus, cultivation at low O_2 can enhance the immunosuppressive properties of MSCs by modifying their functional state, including the cytokine production, expression of surface molecules, and ROS level. *The work was supported by grant RFBR 18-015-00461, and grant of the President of Russian Federation MK-2976.2018.*

DER P 1, DER P 2, DER P 23 HOUSE DUST MITE MAJOR ALLERGENS SENSITIZATION PROFILE IN A PORTUGUESE POPULATION

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Introduction: House dust mites (HDM) represent one of the most important inducers of respiratory allergies worldwide, 85% of allergic asthmatic children being sensitized and higher specific IgE levels being related to likelihood of developing asthma and its severity. The aim of this study is to characterize a Portuguese population of HDM allergic patients concerning major allergens sensitization profile and its clinical relevance. ***Methods:*** Sera of 98 paediatric and adult HDM-allergic patients, living in different country areas, with positive IgE to Dermatophagoides pteronyssinus total extract, were tested for Der p 1, Der p 2 and Der p 23 reactivity. Chi-square Test was used to compare frequencies and T Test to mean IgE values. ***Results:*** All patients had allergic rhinitis, 81% also asthma. Prevalence of IgE to each Der p 1, Der p 2 and Der p 23 was >85%. Overall, 73 patients were sensitized to all three components, 16 to only two, 5 to just one (Der p 23 in 4 of them) and 4 to none. Patterns of IgE to Der p 2 and Der p 23 were similar encompassing adults and children, but Der p 1 reactivity was more frequent in children (91% *vs* 70%, p=0,032). Also in paediatric group, mean IgE values were higher to all components, being significant for Der p 1 and total Der p (56 vs 11 kUA/l, p=0,012; 109 *vs* 48 kUA/l, p=0,018). No sex-related difference was found. Asthmatic patients in general had more frequent IgE response to Der p 1 (91%) and Der p 2 (89%), than nonasthmatics (68%; 68%, respectively: p=0.009; p=0.028). They also had higher mean IgE levels for total Der p (108 *vs* 56 kUA/l, p=0,045). Asthmatic children who had started symptoms after 3 years old (32%) showed IgE values significantly higher than the others (Der p 1, p=0,001; Der p 2 and Der p 23, p=0,005). Furthermore, IgE levels to total Der p and Der p 2 were higher in children with more severe asthma (p=0,007; p=0,045). ***Conclusion:*** High IgE binding to Der p 23 was in accordance to most of studies. Also, subjects without IgE to Der p 1 or 2 had IgE against Der p 23. Children were more frequently sensitized and had higher IgE to Der p 1. Asthma was related to more frequent and higher recognition of Der p 1 and 2 and severity in children seemed associated to higher levels to total Der p and Der p 2.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

ATOPIC DERMATITIS AND SKIN MICROBIOME

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Atopic dermatitis (AD) is a chronic inflammatory disease with the periodic exacerbation and remissions. Long term treatment with various kind of topical and systemic medications causes the subsequent side effects. And it's very important to find the way how to treat AD by the low dose of topical corticosteroids and other medications. Emollients are a cornerstone for background therapy and a maintained treatment in atopic dermatitis. Especially those that can protect the normal flora of skin.

The study was based on the view that the skin has the specific microbiome. They protect our body and is responsible for human physiology. Microbiome is forming at the the start of infant's life, it depends on the way of delivery and also how is close the contact between infant and mother.

Atopic dermatitis causes the change of microbiome. For healthy skin is characterized the higher grade of variety of micro flora then for atopic skin. The low grade of microbiomes is the marker for atopic dermatitis. For effectiveness of treatment is highly important the strength of skin barrier and normal microbiome of the skin.

Therefore, for choosing of background therapy for atopic dermatitis we should prefer the moisturizers which can regenerate of skin microbiome. Combination - topical corticosteroids + emollients (which has possibility to regenerate of skin microbiome) promotes releasing of exacerbation and avoid patient for long term treatment with topical corticosteroids. To use this kind of moisturizers during the remission as a component of proactive therapy help us to prolong the remission. To identify which particular skin microbiome improving moisturizers should be used in each cases of AD is the main goal for future researches.

EMOTIONAL INTELLIGENCE AND CHILDHOOD ALLERGIES

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Prevalence of allergic diseases increases throughout the world. Allergic diseases strongly influence the quality of life of affected children and their family. Many studies have shown the correlations between allergic diseases and emotional disturbances in affected individuals. Disturbances in emotional balance, child's reduced own-perception of well-being and life satisfaction impact the emotional intelligence. The purpose of our study is to measure the emotional entelligence in the children with allergic diseases.

ANALYSIS OF TLR9-INDUCED EXPRESSION OF CYTOKINES TGF-B AND TNF-α IN DIFFERENT ASTHMA PHENOTYPES

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Introduction: Asthma as heterogenous disease is characterized with numerous clinical phenotypes, which can be classified in two groups: Th_2 and non-Th_2 asthma. In contrast to Th_2, non-Th_2 asthma remains poorly understood phenotype, in which control of disease can be hardly achieved. An important role in asthma pathogenesis plays receptors of innate immunity – Toll-like receptors (TLR), which direct the differentiation of immune response. In recent time these receptors have been developed as new targets for asthma immunotherapy. Two molecules involved in asthma pathogenesis, TGF-β and TNF-α, can be potential markers of such TLRs activation. ***Aim***: To evaluate the balance of TGF-β and TNF-α and their TLR9-induced expression in peripheral blood mononuclear cells (PBMC) of patients with different asthma phenotypes. ***Methods:*** Asthma patients (n=13) undergoing inpatient treatment in Internal Medicine Department in University Hospital №1 were included in this study, the group of control consisted of healthy volunteers (n=13). PBMC were isolated by gradient density separation over Ficoll-Urografin and incubated with TLR9 ligand (ODN2336) (Syntol, RF). Expression levels were assessed in dynamics at 1, 4, 12, 24 and 48 h after challenge with ODN2336. Following procedures were performed: RNA extraction (RIBO-sorb, Amplisens), reverse transcription reaction (RT-1, Syntol) and qRT-PCR (PCR-kit, Syntol). ***Results:*** In Th_2 asthma group constitutive expression of TGF-β was almost not observed, while in non-Th_2 asthma group it was detectable in 75% of samples. TLR9-induced expression of TGF-β was higher in Th_2 asthma group than in non-Th_2 (in 300 and 185 times respectively). Constitutive expression of TNF-α was higher in non-Th_2-group, however the induction of expression was observed in neither of asthmatic groups. In control group there were no significant changes in expression levels of TGF-β and TNF-α in intact PBMC, while PBMC exposed to ODN2336 (80% of samples) had highest expression of TGF-β at 1 h, and expression of TNF-α (70% of samples) – at 24 and 48h. ***Conclusion:*** Difference in the levels of TGF-β and TNF-α gene expression in PBMC in определенный?(сорри, уже мозг закончился) asthma groups indicates on immunomodulatory effect of TLR9 ligand, which can be effectively used in personalized asthma therapy.

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THE ROLE OF GROWTH FACTORS IN THE PATHOGENESIS OF ASTHMA IN CHILDREN: GENETIC AND CLINICAL ASPECTS

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Bronchial asthma (BA) is a multifactorial disease that is caused by a complex of neurohumoral and genetic factors. A special role in its pathogenesis is played by tissue growth factors: transforming growth factor β1 (TGF β1) and vascular endothelial growth factor (VEGFA), which has a significant impact on the processes of maintaining and inhibiting allergic inflammation in the respiratory tract. Therefore, the study of changes in the concentration of these factors in the blood serum and features of their inheritance is of great scientific and practical interest. Analysis of associations of polymorphic loci of the gene Arg25Pro C634G TGF β1 and VEGFA gene with the risk of developing the disease were conducted to assess the involvement of genes of growth factors in the pathogenesis of BA. DNA samples were isolated from peripheral blood leukocytes of 30 patients with BA and 27 children of I and IIA health groups. Determination of polymorphic variants of the studied genes was carried out by the method of Allel-specific polymerase chain reaction using sets of SNP-Express reagents. Blood tests for immunological parameters were performed by enzyme immunoassay using human TGF beta 1 Platinum ELISA and Human VEGF-a Platinum ELISA kits (Austria). It was found that in children with BA the concentration of TGF β1 (116.21±51.59 PG/ml) was significantly increased, compared with the control group – 2.70±0.12 PG/ml (p=0.01). There was also an increase in the level of VEGFA in the blood serum of patients (133.59±19.53 PG/ml). The level of tissue growth factors correlates with the severity of the disease and the indicators of respiratory function. The identified association of SNPs Arg25Pro and Tgfß1 gene polymorphism C634G VEGFA gene with an increased risk of developing the disease. Frequency of alleles and genotypes Arg25Pro gene of TGF-β1 in patients with BA were statistically significantly different from children in the control group (χ2 0,05). It is established that the genotype ArgArg of the gene TGF-β1 is associated with increased risk of development of BA in children (OR made up 5.38). The obtained data allow to diagnose the predisposition to BA and to develop a set of preventive measures taking into account the individual characteristics of each patient.

STRATIFICATION AND TREATMENT OF NON TYPE 2 SEVERE ASTHMA

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According to GINA Asthma is defined by history of respiratory symptom that vary under time and in intensity, with variable airflow limitation. Asthma is problem for all country regardless of level of development. But most asthma related deaths occur in lower and lower-middle income country. Risk factor for developing asthma are inhaled substance and particles that provoke allergic reaction. T2-low asthma? Pancigranulocytic asthma & Neutrophilic asthma. Have late onset, not affected by presence of possible allergen, low FEV, more air trapping. Biomarkers are No increase in IgE, Lower FeNO level (<25 ppb), higher level on IL17 and Th17 but no Th2 biomarker. Diagnostic test is different like FeNO level (Differentiate b/w Th2 low or Th2 high asthma), Spirometer, Chest XR, Sputum analysis. For treatment ICS and LABA are less effective and microlides reduce neutrophilia associated airways inflammation. New Generation Drugs are there like Biologics that is medical product made from variety of natural source, use to treat or cure medical conditions. Such as Amalizumab (for Anti IgE), Reslizunab and Mepolizmab (for anti ILS). Macrolides are also use for adult with persistent symptomatic asthma. Thromboplastic can be use but in very few selected patients. ***Conclusion:*** (1) Diagnosis and treatment for Th2-low phenotype isdifferent. (2) Paucigranulocytic asthma is usually the expression of controlled inflammation. Severe patients with paucigranulocytic asthma should be treated with triple therapy and eventually with thermoplasty. (3) Neutrophilic asthma is often severe and unresponsive to conventional therapy. Treatment of neutrophilic asthma should be chosen according individual objectives and treatable traits. (4) Azithromycin is a good option for those with persisting exacerbations. (5) Thermoplasty can be attempted in refractory patients.

EPIGENETICS OF INNATE IMMUNE RECEPTORS AND THEIR ROLE IN BRONCHIAL ASTHMA

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Introduction: Asthma is one of the most prevalent chronic noncommunicable respiratory diseases. Components of innate immunity, especially pattern recognition receptors such as Toll-like receptors (TLRs) 2 and 4, play a critical role in this pathology. The evidence shows that receptors` expression profiles change due to pathogenic pathway. However, the underlying mechanism of these modifications is unclear. Presumably, methylation in promoter sites could change the gene expression profile. ***Aim:*** To compare methylation and expression levels of receptors in pediatric patients with asthma and to define a correlation between methylation status and the incidence of the disease. ***Methods***: Scrapings from the mucous membranes of the upper respiratory tract were taken from 43 children up to 7 years old. They also were devided in 3 groups: patients without any allergic or autoimmune disorders (16), children with moderate (13) and severe (14) asthma. During the research the following methods were used: DNA extraction, sodium bisulfite conversion, methylation-specific PCR, restriction, detection, and statistical evaluation methods (Fisher exact test). ***Results.*** Based on data for methylation, it was found

International Journal on Immunorehabilitation
2019 Volume 21 No 1

that the rise of unmethylated sites influenced the increase of gene expression, which lead to moderate/severe asthma development by activation of TLRs. Healthy patients got methylated or partially methylated regions in 50% of cases. There was an increase of incompletely methylated sites in children with moderate asthma; a small amount of unmethylated regions appeared in patients with severe asthma. The same situation also held for methylated promoter sites in TLR4. But in that case the amount of unmethylated parts became bigger and occurred in all 3 experimental groups. ***Conclusion:*** According to data for methylation status of significant innate immune receptors the early case detection and prognosis of mentioned respiratory pathology might be performed.

PLACE OF TOPICAL OF ANTIHISTAMINIC PREPARATIONS AT A SEASONAL RHINALLERGOSIS

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The actual problem of modern otorhinolaryngology is the rational therapy of seasonal allergic rhinitis (SAR). Realizing that the most effective method of treatment of allergic diseases with a polyvalent sensitization in patients with allergic rhinitis (AR) is allergen-specific immunotherapy, under the condition of holding not less than 3 courses, otolaryngologists have in the manifestation of symptoms of mild to moderate severity to oversee this category of patients. The aim of the work is to study the comparative effectiveness of topical therapy of seasonal allergic rhinitis In the course of accounting for the dynamics of relief of the main symptoms, the results were obtained, allowing to speak about the comparable effectiveness of topical therapy with SAR GCS and antihistamines, in particular mometasone furoate (nasonex) and topical combined blocker of H1–histamine receptors long-acting loratadine with recombinant human alpha-2b interferon (Allergoferon). In this case, Allergoferon characterizes the rapid onset of action (within the first 15 minutes), resulting in the severity of pathological symptoms is rapidly reduced. The effectiveness of the drug is clearly manifested by the 3rd day of administration and gradually increases by the 7th-14th day, which allows it to be used as a monotherapy, while THCS due to the peculiarities of their action is advisable to appoint as the main component of combination therapy with the gradual abolition of other drugs as the symptoms of ATS subside. Rapid positive dynamics of relief of acute symptoms of ATS allows patients to independently from 3–5 days to switch to a double reception. The presence of recombinant alpha-2b interferon with immunomodulatory effect does not exclude the possibility of using the drug without taking into account the microbial background of SOPN, but this issue requires further study. The drug has a good safety profile, in the appointment, like any drug, should take into account individual hypersensitivity to its components. The use of loratadine in the form of gel for intranasal and eye application expands the possibilities of effective and safe therapy of ATS, including with conjunctival manifestations.

EFFECTS OF TITANIUM DIOXIDE NANOPARTICLES ON IMMUNE RESPONSE AND FOOD ALLERGY DEVELOPMENT

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Background: Titanium dioxide (TiO_2) is a widespread white food pigment and often added to pharmaceutical products and cosmetics, continuously entering the human body (0.5–1.1 mg/kg bw in adults, 1.4–3.2 mg/kg bw in children) in particles 30–300 nm diameter size.

Objective: To evaluate the intestinal and systemic effect of TiO_2-NPs on the immune response in naïve organisms and to analyze the influence on a development of food allergy.

Methods: Female BALB/c mice were fed TiO_2-NPs with or without pre-absorption to Bovine serum albumin (TiO_2-NPs+BSA) for 14 days intragastrically. Thereafter, mice were either sacrificed to evaluate the immune response after oral TiO2-NPs gavages or sensitized to the egg allergen Ovalbumin (OVA) with concomitant acid-suppression.

Results: We observed slight elevations of total IgA levels in the intestinal lavages of animals fed with TiO_2-NPs+BSA or pure TiO_2-NPs compared to naive animals, however without reaching statistical significance. Spleen cells of mice that received either TiO2-NPs or TiO_2-NPs+BSA after 72 hours of incubation with a solution of TiO_2-NPs or TiO2-NPs+BSA secreted a higher amount of interleukin 10 than the cells of the control group of mice ($p<0.01$, $p<0.05$). The spleen cells of mice fed with TiO_2-NPs after 72 hours of incubation with a solution of TiO2-NPs secreted a higher amount of IL17a than the cells of the control group of mice ($p<0.01$). In the group of mice receiving only BSA, the secretion of IL10 and 17a after stimulation with solutions of TiO_2-NPs or TiO2-NPs-adsorbed to BSA was not statistically differ from the control group. In mice, sensitized with OVA, systemic allergen challenges induced a significant drop of body temperature and higher levels of mMCP1 in serum, higher levels of OVA specific IgE and IgA antibodies in intestinal lavages of sensitized animals pretreated with TiO2-NPs or with BSA compared to naïve mice ($p<0.05$), but not in animals pretreated with TiO_2 NPs-adsorbed to BSA.

Conclusion: These data indicates that binding of TiO_2-NPs to proteins can change the immunogenic characteristics of TiO_2 and influense allergy development. Thus, our work represents an important contribution to current research efforts evaluating the safety of TiO_2-NPs ingestion.

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THE RISK FACTORS ASSESSMENT OF PERMANENTLY RECURRENT COURSE OF ATOPIC DERMATITIS IN CHILDREN

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The increasing of allergic disease's prevalence and allergic disease's severe forms acceleration set up the allergy problem on one of the first places in present clinical medicine.Among the skin allergic diseases in children the most spread is atopic dermatitis(AD).Despite widespread introduction of local anti-inflammatory therapy,the high percent of patients with permanently recurrent disease course(PRDC) persists steady. ***Purpose***: To reveal the significant risk factors of AD severe forms formation in children with PRDC. ***Results:***The comparative assessment of AD clinical course and features was carried out in children aged from 4 months to 3 years who were on treatment at the department of allergology of N.N. Silisheva regional children's hospital from 2014 till 2017 years with the statistical analysis and the identification of correlation (r) between risk factors and the formation of PRDC.The main group consisted of 36 patients of early age with a severe form of AD;the comparison group consisted of 43 children with mild disease severity.According to the results, it was revealed that during this time the frequency of hospitalizations of early age children increased-patients with permanently recurrent course of AD (28%).The ELISA and PCR diagnostics in 45 out of 79 examined patients of early age confirmed the presence of bacterial or mixed infection(56.9%).Weighed allergic anamnesis had a more significant matrilineal relationship than the patrilineal ($r=0.48$, $p<0.001$and $r=0.34$, $p<0.05$). The additional factors of PRDC of AD were gestosis of pregnancy ($r=0.32$, $p<0.01$) constant threat of abortion($r=0.49$, $p<0.001$), recurrent ARVI and bronchitis in first year children($r=0.49$, $p<0.01$), signs of intestinal dysbacteriosis ($r=0.52$, $p<0.001$). ***Conclusions:***The analysis showed a steady increase in the frequency of hospitalizations of children with PRDC of AD,children with early clinical manifestation,the absence of positive clinical dynamics against baseline therapy due to the presence of secondary infection with bacterial or mixed flora.The formation of complicated AD forms was caused by a complex of risk factors (family weighed anamnesis in allergic and non-allergic diseases,complications during pregnancy, recurrent infectious diseases and intestinal dysbiosis).

PROGNOSTIC SIGNIFICANCE OF FRACTALKIN LEVEL IN CHILDREN WITH ATOPIC DERMATITIS

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Introduction: Fraktalkin (CX3CL1), belonging to the family of chemokines, plays an important role in "attracting" basophils, eosinophils, leukocytes and mast cells to the pathological focus, which activates the adhesion of cells to the vascular endothelium, followed by migration into tissues and the release of mediators, and an inflammatory reaction of different genesis. Objective: to establish the prognostic value of the CX3CL1 level in the serum of children with atopic dermatitis (AD), depending on the severity level and the concomitant pathology of the gastrointestinal tract. ***Methods***: The level of CX3CL1 in 100 children with AD with a pediatric form of the disease and comorbid pathology of the gastrointestinal tract (including giardiasis, reactive pancreatitis), preschool age, with the informed voluntary consent of the parents was studied. In the comparison group there were 50 children with AD, without gastrointestinal tract pathology, in the control group-20 somatically healthy children. The statistical processing of the results was carried out with the help of statistical program Statistica 12.0 ("StatSoft, Inc.", USA). The level of CX3CL1 was assessed by an enzyme immunoassay using sets for the quantitative determination of CX3CL1 in biological fluids "RayBio® Human Fractalkine" ("RayBiotech, Inc.", USA). ***Results:*** As a result of the study, a significant increase in the level of CX3CL1 in the group of children "AD + reactive pancreatitis + giardiasis" was found in comparison with the group of children "AD without pathology of the gastrointestinal tract" and the control group – median [25; 75 percentile] 170.95 [137.8-203.3] *vs* 102.7 [83.2-155.85] *vs* 25.7 [22.6 –36.8] pg / ml; $p=0.0005$. ***Conclusions:*** An increased production of CX3CL1 was revealed, the level of which determines the severity of AD by the principle of direct correlation dependence. It was found that the combination of blood pressure and gastrointestinal pathology is accompanied by pronounced changes in the level of CX3CL1 compared to those in atopic monopathology, which indicates the activation of a systemic inflammatory response, which can be of significant importance in the immunopathogenesis of atopic disease.

DEVELOPMENT OF CRITERIA FOR INCLUSION OF VITAMIN D IN COMPLEX THERAPY OF PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA BASED ON A STUDY OF VITAMIN D METABOLISM

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Actuality: more than half of all patients with chronic spontaneous urticaria (HSU) are resistant to antihistamine therapy, which requires the search for alternative treatment methods. ***The aim of the study:*** A complex assessment of the content of the main metabolites of vitamin D and their receptors in patients with HSU and to establish indications for the use of vitamin D in HSU therapy. ***Methods:*** The study included 126 patients with HSU and 61 healthy donors who determined the serum concentration of 3 metabolites of vitamin D – D2, 25(OH)D, 1,25(OH)2D, vitamin D receptors (VDR) of mononuclear blood cells. For 4 weeks, 50 patients in addition to basic therapy received cholecalciferol 10000 U/day. The activity of HSU was assessed according to the UAS-7 scale. To calculate the significance level (p), the Mann-Whitney and Wilcoxon criteria were used. Results: hypovitaminosis D (25(OH)D<30 ng/ml) was detected in 54.2% of patients. In the presence of hypovitaminosis D, the activity of HSU is higher than at a normal level of vitamin D (UAS-7 – 24.3±3,95 and 17.5±2.87,

International Journal on Immunorehabilitation
2019 Volume 21 No 1

p<0.05). Negative correlation between UAS-7 and 25(OH)D is present in patients with hypovitaminosis D and is absent at normal level of vitamin D. The concentration of metabolites of vitamin D (D2, 1.25(OH)2D) and VDR in patients corresponded to the data in the control. The therapy with cholecalciferol in patients with hypovitaminosis D resulted in a decrease in UAS-7 from 24.3±3.95 to 15.8±3.01 (p<0.05), in patients with a normal level of vitamin D UAS-7 did not change significantly. The use of cholecalciferol reduced UAS-7 in patients with severe HSU activity from 37.2±1.06 to 22.4±2.65 (p<0.05) and moderate activity from 20.7±0.58 to 14.4±1.29 (p<0.05). In patients with mild activity of disease UAS-7 did not change. Conclusions: 1. In 54.2% of patients with HSU, a reduction of 25(OH)D was observed, while the levels of other metabolites (D2, 1,25(OH)2D) and VDR were consistent with the data in the control. 2. In patients with hypovitaminosis D, urticaria is more active than in patients with normal vitamin D levels, and there is a negative correlation between 25(OH)D and UAS-7. 3. The criterion for the inclusion of vitamin D in patients with severe and moderate HSC is a low level of 25(OH)D.

EXPERIENCE WITH OMALIZUMAB IN THE TREATMENT OF CHRONIC URTICARIA. DESCRIPTION OF THE CASE AND LITERATURE REVIEW

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The purpose of the study: a review of the literature devoted to the treatment of chronic urticaria with the drug Omalizumab for the last 5 years, the examination of the clinical case. M***ethods***: the publication of the electronic catalog of the republican medical library and information center is used. The search was carried out according to: chronic urticaria, omalizumab. Results of the study: it was found that urticaria is diagnosed in 15–25% of people in the population, with a quarter of cases accounted for chronic urticaria (HC). Up to 60% of patients with HC suffer from an autoimmune form of it. Autoreactivity in patients with CK is currently divided into two subtypes: the appearance of IgG autoantibodies to FcεRI receptors and the emergence of IgE to autoantibodies. Omalizumab, representing recombinant humanized monoclonal anti-IgE antibodies, binds free IgE and, forming a biologically inert molecule, reduces the likelihood of their interaction with mast cells. Patient K., 64 years old, turned to the GCA of Kazan with complaints of multiple red blister rashes all over his body. He considers himself sick from 2010, when he first noticed such elements on his hips. During 7 years, acute urticaria, chronic recurrent urticaria was hospitalized many times. For several months, K. received therapy with modern H1-blockers at 1t / day, then with an increase in the dose to fourfold intake according to the second-line therapy scheme, for 4 weeks without significant therapeutic effect. So, with the last hospitalization on the scale of activity of rashes and itching of UAS7, the patient noted 6 points for the day (out of 6 maximal) and 36 points for the week (out of 42 maximal). The IgE level at that time was 16.56 IU/ml. In November, 300 mg of omalizumab was injected subcutaneously. Within 1×day the amount of rashes was reduced, after 48 hours the elements disappeared completely. The patient did not notice any undesirable effects. The level of IgE total at discharge is 92.18 IU/ml. A sample with an autologous serum is positive. Conclusion: The drug Omalizumab is an effective pathogenetic therapy for chronic urticaria; during the therapy, skin reactivity does not change; Omalizumab may be the drug of choice for chronic urticaria with a normal level of IgE total.

ALLERGIC RHINITIS, BRONCHIAL ASTHMA, ATOPIC DERMATITIS IN CHILDREN'S POPULATION

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Aim: Study of prevalence of allergic diseases and risk factors in the children's populations of Georgia (2017–2018). ***Methods:*** Group to be studied included 899 children from 1–14 (girls – 51.8%; boys – 48.2%). At the first stage of epidemiological study the large-scale work was performed, including screening of 1899 children through questionnaire completed directly at a time of interviews with the parents. Information was further specified through telephone interviews. Key data of the screening questionnaire were directed towards initial diagnostics of allergic diseases. At the same time, the screening questionnaire implied, at the first (population) stage of the studies possibility of identification of the potential risk factors (questionnaire included information about obstetrics anamnesis, data about child's development before one-year age and further etc.) and these data were further specified more precisely through expanded questionnaire of epidemiological study of allergic diseases. On the second stage of epidemiological studies part of the patients with allergic diseases (315 children) were subjected to clinical-allergological study. At the same stage external respiratory function was studied, general IgE level in the blood and prick-testing was conducted, study of external respiration function. At the last stage of epidemiological and clinical-laboratory study mathematical-statistical data processing was provided by means of software SPSS/V12.5 (Statistical Package for Social Sciences). ***Results:*** Screening showed general characteristics of the studied population. In the population number of girls exceeded the one of boys (p<0.001), especially within the age group from 7 to 14 years. According to the results of questioning, for 12 months, symptoms of allergic rhinitis (rhinorrhea, sneezing, nose itch, nasal obstruction and eyes' itch) were identified in 16.7 of population (p<0.05); symptoms of bronchial asthma (wheezing (9%), coughing episodes at night (5.7%), intolerance to physical load (3.9%), indoor and outdoor episodes (11.2%), episodes of coughing

ISSN 1562-3629

and rales in response to stimulus (7.2%)) were identified in 9.8% of the population; atopic dermatitis (dermatitis, itch, revelation in early age, involvement of large areas in early age, damage of extremities bending and stretching surfaces in adults) – 4.9% ($p<0.01$); food allergy – 9.7% ($p<0.001$) etc. At the second stage of clinical studies, on the basis of prick-testing, average IgE, in our case, was 1–4 times greater than normal level. Results of study of allergens showed sensibilization to domestic dust (D.F. and D.P.) (75, 04%) ($p<0.05$). In 24.96% of cases there was stated sensibilization conditioned by cat and dog epidermal allergens.

TARGET IMMUNOTHERAPY IN IMMUNOCOMPROMISED CHILDREN WITH COMORBID DISEASES

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Comorbid diseases in individuals with secondary immunodeficiency have common pathogenetic relationships aggravate diseases course and make it difficult to treatment which requires allow immunopathogenesis features in immunotherapy. ***Aim:*** value of combined immunotherapy programs effectiveness in immunocompromised children with comorbid diseases targeting features of immunopathogenesis. ***Methods:*** In research there were children with clinical criteria of secondary immunodeficiency with recurrent respiratory infections (RRI) 10 or more times a year: 1 gr – 14 children with RRI and herpes virus infections – HVI (HSVI/II, EBV, CMV, HHVVI) (5–8 years old); 2 gr-14 girls with RRI and recurrent chronic nonspecific vulvovaginitis (CNV) (3–4 years). Control-healthy children: 1 gr (n=20), 2 gr (n=12). We investigated features of antiviral and antibacterial immunity mechanisms outside the acute period of diseases before and after therapy. ***Results:*** Children had mainly combined defects of immune system with predominant neutrophilic granulocytes (NG) disorders (defects of phagocytic and killing functions) in groups. In 2 gr. was decrease of 1.5–2 times in Ig(A,G,M), which helps to maintain inflammatory process, creates prerequisites for frequent exacerbation of CNV. In 100% of cases, defects were found in IFN system-decrease in IFNα,γ (gr1) or decrease in IFNα and lack of adequate increase in IFNγ on viral load (gr 2). Targeted combination immunotherapy with recombinant IFNα2b inclusion mixed with antioxidants (Viferon) for IFN status correction, glucosaminylmuramyldipeptide for correction of NG disorders. In gr1 was carried out antiviral therapy against HVI – inosine pranobex. Thus, the frequency of RRI decreased by 2.5–5 times, exacerbations of CNV by 3,4 times and HVI load. Effects of defective NG recovery, humoral immunity, IFN have been achieved. ***Conclusion:*** Targeted use of combined immunotherapy demonstrates a positive clinical, immunological and protective effects in immunocompromised children with comorbid diseases.

THE EFFECT OF PLACENTAL SECRETORY FACTORS ON NK CELL FUNCTION AND PHENOTYPE

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Introduction: Natural killers (NK cells) play a major role in the host-rejection of both tumors and virally infected cells. During pregnancy, a new unique population of NK cells appear in the maternal-fetal interface, which are called decidual NK cells (dNK cells). During pregnancy, dNK cells are found to take part in angiogenesis, cooperate with trophoblast cells, control trophoblast cells invasion. ***Aim:*** To investigate changes in NK phenotype and functional activity in presence of placental secretory factors in in vitro model. Material and methods: Assessment of NK cells transmigration activity was made using Boyden chamber assay. On the first day, we added EA.hy926 cells in the upper chamber. On the second day, we added NK-92 cells into the upper chamber and supernatants from placentas were added into the lower chamber. Placentas were obtained: after induced abortion at normal 1st trimester pregnancy (1TP) and after caesarean section at normal 3rd-trimester pregnancy (3TP). After 24 hours number of migrated NK cells in lower chamber was measured, using flow cytometer FACSCanto II (BD, USA). NK cell cytotoxicity was assessed by measuring dead JEG-3 cells after their co-cultivation with NK-92 cells, using flow cytometer FACSCanto II (BD, USA). Results: 1TP and 3TP supernatants halved number of migrated NK cells twice ($p<0.001$) compared to NK cells that migrated without secretory factors. Among NK cells that migrated in the presence of 1TP supernatants there were more cells with expression of CD11a and CD11c ($p<0.001$), but less cells with expression of CD11b ($p<0.05$). 1TP supernatants induced NK cell cytotoxicity against trophoblast cells ($p<0.001$). ***Discussion:*** 1TP supernatants may play role of repellents during NK cells transendothelial migration. The also change NK cells phenotype. At the same time, 1TP supernatants induced NK cell cytotoxicity against trophoblast cells. *Funding: President's grant NSh-2873.2018.7, President's scholarship SP-2836.2018.4.*

CORRELATION OF INDICATORS OF SYSTEMIC INFLAMMATION AND LIVER FUNCTION WITH THE SEVERITY OF SKIN DISEASE IN PATIENTS WITH SEVERE FORMS OF PSORIASIS

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Objectives: Compare leukogram indices in patients and to evaluate the effect of different factors on the indices of liver function in patients with severe forms of psoriasis (Ps) and psoriasis arthritis (PsA). Material and methods: 164 (100%) pa-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

tients with Ps (92 male (56.8%)/72 female (44.4%)). Only skin manifestations of Ps were in 137 (83.5%) out of 164 patients, PsA was registered in 27 (16.4%) out of 164 patients. Mean age of Ps patients was 42.3±14.6 years, with PsA – 54.0±14.0 years, mean PASI>10. All patients were divided into age groups, according to the World Health Organization's standard. M±m, t-test, (%) were calculated. The indices of liver function in patients with severe forms of psoriasis (Ps) and psoriasis arthritis (PsA) were calculated. All $p<0.05$ were considered to indicate statistical significance. Results: The mean level of leukocytes in patients with PsA was $7.8\pm2.4\times10^9$l; erythrocyte sedimentation rate (ESR) – 14.3 10.5; neutrophils – $60.0\pm10.2\times10^9$/l; lymphocytes – $28.5\pm8.9\times10^9$/l. The mean value of the level of leukocytes in patients with Ps was 6.7 2.3×10^9/l, ESR -14.4 10.6; neutrophils – 60.8 10.4×10^9/l; lymphocytes – $28.1\pm8.8\times10^9$/l. No significantly differences were found in the leukogram and ESR in patients with Ps and PsA in all age groups. The level of the ESR were more in 2 times in significantly more cases in PsA compare Ps patients in age group 44-60 years. In patients with cutaneous psoriasis who used methotrexate for a long time, AST values were 35.0 13.3, ALT (alanine aminotransferase) scores were 16.5 6.3. In patients with PsA who received long-treatment with methotrexate, the AST (aspartate aminotransferase) values were 36.2 15.9, and the ALT scores were 32.3 16.8. In patients with cutaneous psoriasis who abused alcohol, ALT scores were 34.3 16.8, while AST scores were 30.9 17.9. In patients with PsA who abused alcohol, the ALT values were 43.5 13.7, the AST values were 43.5 30.1. Conclusion: Leukogram indicators don't reflect the severity of the skin process and don't depend on age and sex. The highest indices of inflammatory markers (ESR) were found in patients with PsA in the age group of 44–60 years. According to the results of the study, we found a significant increase in aminotransferases in patients with severe forms of psoriasis. Long-term use of methotrexate and alcohol consumption have a great effect on the increase in liver enzymes.

ULTRA HIGH FREQUENCY REFLEXOTHERAPY IN REHABILITATION OF PATIENTS WITH ALLERGY FORM VASOMOTOR RHINITIS

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Purpose of the study. Improving the effectiveness of the rehabilitation of patients with allergic vasomotor rhinitis (AFVR), the development of more physiological and effective in operation methods of ultrahigh-frequency reflexotherapy (UHF RT), the technical means of their provision and implementation in the practice of allergology seems relevant. ***Methods***. Diagnostic and rehabilitation studies were carried out in 43 patients with allergic and neuro-vegetative forms of vasomotor rhinitis (NVFVR). To improve the efficiency of rehabilitation of patients with AFVR, we have proposed, successfully tested and introduced into clinical practice a more physiological, highly effective UHF RT method with the original "RELIT" device that has no analogues in the world. Used acupuncture points (AP): VG 24, VB 14, V 1, V 2, VG 26, GI 20, E 1, E 2, BM 3, BM 14, BM 15, BM 16, PC 14, PC 15, PN 42 and others. If patients have a comorbid pathology, the corresponding antibodies were additionally included in the formulation. ***Results***. In the analysis of clinical and paraclinical data after 4–5 sessions of UHF RT, a regression of the symptoms of vasomotor rhinitis and autonomic disorders was noted. By the end of the course of rehabilitation, a positive effect on AFVR was observed in 71% of patients, with NVFVR - in 95% of patients. UHF RT sessions are carried out painlessly, atraumatic, aseptic, effective, well tolerated by patients. There were no adverse reactions in all patients. ***Conclusion:*** UHF RT has proven to be effective in AFVR. The UHF RT method itself corresponds to its medical purpose. The device "RELIT" is distinguished by high operational technical characteristics. It seems promising to continue using the UHF RT method for complex rehabilitation in allergology.

PROTEOMIC PROFILING OF LIZATE FRACTIONS OF NATURAL KILLERS OF NK-92 LINE AND MICROVEALS PRODUCED BY THEM

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Natural killer cells (NK cells) are key cells of the innate immune system, providing the first line of defense against various infectious agents and playing an important role in the mechanisms of antitumor resistance. The microvesicles (MVs) produced by them can participate in the regulatory and cytotoxic activity of NK cells. The role of MVs in the immune response and their protein composition are currently not well understood. The purpose of this study was to investigate the protein profiles of NK cells and their MVs. The NK-92 cell line, reproducing the main characteristics of NK cells, was cultured in a full growth medium based on α-MEM. For the isolation of cells and their MVs, the culture was subjected to differential centrifugation (200g, 9900g, and 19800g). Lysates were fractionated on OFFGEL High Resolution IPG Strip (24 cm, pH 3–10) in a 3100 OFFGEL Fractionator chamber (Agilent Technologies, USA) in the mode of active rehydration and subsequent separation at a voltage of 200–3400 V (20ºC, 24 h). The resulting protein fractions were trypsinized, with mass spectra of tryptic peptides obtained on an Axima Resonance MALDI mass spectrometer (Shimadzu/Kratos Analytical Ltd., United Kingdom). Protein identification was performed against the SwissProt and NCBI databases by the taxonomic constraint for Homo sapiens using the peptide fingerprinting method in the Mascot program. Using the isoelectric focusing me-

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thod, 24 fractions were obtained with different content of identified proteins in the selected acid-base range. The total of 463 proteins (including isoforms) were identified: 180 proteins were detected in cells and 290 in MVs, six proteins being identified in both cells and MVs. All of the identified proteins were combined into 32 functional groups, of which cytokines, intracellular signaling proteins, transcription factors, intercellular signaling proteins and apoptosis regulating proteins are of the greatest interest. *Supported by RFBR grants (projects #17-04-00679 and #19-015-00218).*

INNOVATIVE APPROACHES TO CORRECT CYTOPENIA

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Cytopenias are a serious side effect of the treatment of oncological diseases, which prevents from carrying out an adequate and complete course of chemotherapy and radiation therapy. Neutropenia is the most common hematological complication in cancer patients, manifested by a decrease in the number of granulocyte cells in the bone marrow section. The presence of neutropenia is associated with a high risk of bacterial and fungal infections, and represents a threat to the lives of patients, since, if improperly treated, it can lead to septic shock and death. Glycopeptide bacterial cell walls, which normally form during the breakdown of commensal microflora and support the body's immune homeostasis from the moment of birth, also affect hematopoiesis, adjusting cytopenias of various etiologies. An important circumstance is the presence of the NOD2 receptor localized in the cytoplasm of almost all cells of the body, specific binding to which induces a cascade of reactions that trigger the synthesis of cytokines, including G-CSF. Glucosaminyl muramyl dipeptide (GMDP) provides protection against neutropenia comparable to G-CSF in an experimental model. Researchers from Canada, Russia, France and Japan demonstrated the effectiveness of glycopeptides in the correction of cytopenias and led to the creation of a number of anticancer drugs. An innovative drug – a derivative of muramyl dipeptide (GMDP-A) has successfully passed pre-clinical trials in the implementation of the State program of the Russian Federation "Development of the pharmaceutical and medical industry" 2013–2020 and is currently in the first phase of clinical trials. The advantage of the glycopeptides are the natural mechanism of action, the absence of side effects, low price and the possibility of long-term use.

EFFECT OF CELL AND HUMORAL SENSITIZATION ON PREGNANCY OUTCOMES

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The relevance of the study is determined by the critical demographic situation in the Russian Federation. The frequency of pathology of pregnancy and the associated adverse outcomes for the fetus and newborn child are more than 35%. The main mechanisms mediating disturbances of gestation are changes in the immune system. According to the pathophysiological classification of British scientists Jelle and Coombs, impaired immune homeostasis can be considered in terms of types II and IV of immunopathology. The work carried out presents the mechanisms of disorders in the immune system in women during pregnancy in normal and pathological conditions. The importance of antisperm antibodies (ASA) and cell sensitization (RTML with PHA and placental antigens) has been demonstrated in gestational complications such as the threat of abortion (UPB) and gestosis (OPG – gestosis). The results of the study allowed to confirm the hypothesis of the dominant value of the immune system in the process of carrying full-fledged offspring. The most adverse outcomes were recorded in women with FBR. The incidence of pathology in the group of women with FBR was 94.7%. Death of the fetus / newborn baby was recorded in 29.8% of cases. A more favorable situation has developed in the group of women with gestosis. The incidence of pathological outcomes in this group was 16.6%. The death of fetuses / newborns was recorded only in 12.9% of cases. Perinatal losses in the group with physiological pregnancy amounted to 1.6%. Thus, the conducted studies undeniably prove the role of immunopathological processes (for example, ACA and cell sensitization processes) in the development of the pathology of pregnancy. At the same time, there is a direct link: the higher the frequency of occurrence of ASA and the lower the values determined in RTML with "placental antigens", the heavier the prognosis and outcome of pregnancy. A wider introduction into practice of these markers of autoimmunity will allow applying therapeutic measures at the earliest possible time in order to preserve the pregnancy and prolong it. *The publication has been prepared with the support of the «RUDN University Program 5-100».*

IMMUNOBIOCHEMICAL MARKERS OF DEPRESSIVE DISORDERS IN PATIENTS WITH EPILEPSY FROM THE POSITION OF NEUROPLASTICITY

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The relationship between epilepsy and depressive disorders (DD) is due to the comon pathogenetic neurotransmitter and immunobiochemical mechanisms, as well as the involvement of unified structural and anatomical parts of the brain in the pathological process. Objective: to study the relationship between the nature of metabolic and immune disorders in patients with epilepsy associated with depressive disorders (PED). Materials and methods: the study included 40 patients with PED and 39 healthy volunteers (HV). The identification of DD was made using the scale HDRS. DD of mild severity were re-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

vealed in 17 patients (42.5%), DD of moderate severity – in 23 (57.5%). At the first stage, the ratio of metabolites by MRI spectroscopy of hippocampus: N-acetylaspartate (NAA), choline (Cho), creatine (SG) was calculated, the level of brain neurotrophic factor (Brain-derived neurotrophic factor - BDNF) in the blood was studied. After verification of DD in PED, treatment with antidepressants (AD) from the group of selective reuptake inhibitors was started. The second stage of the survey was carried out after 6 months. Results: At stage 1 of the study revealed a decrease in the level of BDNF and a number of indicators of the ratio of hippocampal metabolites in PED: NAA/Cho=1,3±0,22, NAA/Cr=1,6±0.22, Cho/Cr=1,7±0,11, compared with the HV: NAA/Cho 1,9±0,23; NAA/Cr – 1,8±0,11; Cho/Cr=1±0,1. At the second stage of study, 35 PED (87.5%) showed positive dynamics of the studied parameters (increase of NAA/Cho, NAA/Cr, decrease of Cho/Cr), which indicates an improvement in metabolic processes in the studied parts of the brain, while 5 (12.5%) these results remained virtually unchanged, which can be considered as "negative neuroplasticity". After treatment of AD, an increase of BDNF was observed in all patients, but only in 35 patients the increase reached the level of HV. Positive dynamics of the content of metabolites in the hippocampus and levels of BDNF occurred synchronously in the same PED, which is clinically characterized by a decrease in the severity of DD at the same time, 12.5% of the PED this relationship was not observed.

Thus, the study of the dynamics of biomarkers from the standpoint of neuroplasticity, in the treatment of epileptic patients with DD, can be considered as a predictor of the therapeutic response and determine the choice of therapeutic tactics.

THE ROLE OF STREPTOCOCCAL INFECTION IN THE IMMUNE PATHOGENESIS OF PSORIASIS

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Psoriasis (PS) is one of the most common dermatosis affecting 3 to 7 percent of the world population. The disease has a multifactorial nature with involvement and influence of genetic, immune and environmental factors and is characterized with hyperproliferation of epidermal cells. Immunopathogenesis of PS includes several stages such as: activation memory T-cells and dendritic cells, increased production of TNF-α, IL-1, IL-6, IL-8, IL-15, IL-18, IL-20, IL-23, chemokines launching proliferation and differentiation of keratinocytes and inducing inflammatory response in the dermis. Launching mechanisms for PS development are often chronic foci of infection – tonsillitis and pharyngitis caused by Group A beta-hemolytic streptococcus (BHS). The presence of common BHS proteins and keratinocytes leads to the fact that the immune system perceives «own» for «others», resulting in destruction of their own cells. A clear connection has been established between the guttate PS and the infection of the upper respiratory tract caused by BHS of group A. Intracellular presence of streptococcus ensures protection against immune complexes and antibiotic therapy. Consequently, important direction of modern immunodermatology is not only the establishment of species and antigenic identities of streptococcus in patients with PS of different severity in clinical course, but also the determination of the immunological features of its course.

These studies will help not only to optimize the diagnosis, but to prove the necessity of involvement of immunotropic drugs in complex program of PS treatment, associated with streptococcal infections. *The publication has been prepared with the support of the «RUDN University Program 5-100».*

DETECTION OF HELYCOBACTER PYLORI DNA FRAGMENTS PERIPHERAL BLOOD MONONUCLEAR CELLS

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Material for the research was biopsies from the mucous membrane of gastroduodenal area and peripheral blood mononuclear cells (PBMC) obtained from 77 patients, from which 20 were voluntaries without gastrointestinal tract pathology, 14, with superficial gastritis, 18, with erosive gastritis, 14, with erosive gastroduodenitis, and 11, with stomach ulcer of duodenum. Then, the patients were distributed to some groups depending on the nature of mucous tunic injury as follows: surface inflammation without injury with leukocyte-infiltrated epithelium and destructive inflammation with infiltration and erosive ulcerous injury of mucous tunic. Biopsy material was taken in the morning from fundic and antral parts of stomach, as well as from duodenal cap. Peripheral blood mononuclear cells were extracted with density gradient of ficoll-urografin equal to 1.077, from which CD3+4+, CD3+8+, CD14+ cells were selected by means of immunomagnetic separation. Helicobacter pylori in the biological material were determined by means of polymerase chain reaction. UreC, cagA, and vacA primers for Helicobacter pylori were applied. During the research we have discovered that Helicobacter pylori DNA fragments persist in PBMC. Fragments of genome of ureC coding C-subunit of urease were detected most frequently. The dependence of the evidence of pathology in the mucous membrane of gastrointestinal tract on the circulation of pathogenic agents in peripheral blood was established. Key words: pathology of gastrointestinal tract, Helicobacter pylori, peripheral blood mononuclear cells.

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POSTVIRAL SYNDROME OF CHRONIC FATIGUE AND IMMUNE DYSFUNCTION ASSOCIATED WITH AMNESTIC MILD COGNITIVE IMPIERMENT SYNDROME

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Introduction. Nowadays, the role of the herpesvirus in particular, neuro - immune HGV 6 and EBV,in the etio - and immunopathogenesis of infectious and non-infectious diseases, the clinical picture of which is often atypical and accompanied by the development of post-viral syndrome of chronic fatigue and immune dysfunction, including signs of amnestic mild cognitive impairment syndrome (aMCI), has been proved. The aim of our study was to study the prevalence of aMCI among patients suffering from atypical chronic active mono- and mixed-herpes virus infections (ACA HVI), as well as to identify violations in the antiviral protection system and the interferon system in order to clarify the immunopathogenetic mechanisms of this syndrome, as well as clarifying immunopathogenetic significant violations of the immune mechanisms and antiviral protection of the interferon system. ***Methods:*** We have observed 198 patients aged between 23 and 60 years old, suffering from ACA HVI. The complex of research included traditional clinical and laboratory methods for assessing the activity of HVI (ELISA, PCR), methods for evaluating the functioning of antiviral immunity (ELISA, flow cytofluorimetry). To assess cognitive functioning, we used the CGI scale (Clinical Global Impression), a brief scale of mental status (MMSE, Mini-Mental State Examination). ***Results***. In the evaluation of cognitive functioning it was found that in patients with ACA HVI the frequency of aMCI was 68.3 %. At the same time, in patients with mixed HVI, the frequency of aMCI was high and amounted to 87.4%, while in patients with mono HVI only 12.6%. The study of the main mechanisms of antiviral protection and interferon system revealed defects in the functioning of neutrophilic granulocytes – 82.3%, decrease in spontaneous and induced production of INF-α and ɣ in 96.8%, deficiency of ECC and $CD3^+CD4^+$ subpopulations; $CD3^+CD8^+$; $CD3^+CD56^+$ in 89.5%. ***Conclusion.*** Thus, in patients suffering from ACA-HVI, there is a postviral syndrome of chronic fatigue and immune dysfunction, including signs of aMCI. At the same time in patients with ACA-HVI and aMCI, the combined defects of interferon system and immune system functioning were revealed. The obtained data allowed not only to clarify the immunopathogenetic mechanisms underlying the occurrence of chronic neurodenegerative process in aMCI, but also to identify new directions for the development of a promising therapeutic strategy -– complex targeted interferon and immunotherapy.

EARLY DIAGNOSIS OF BRONCHIAL ASTHMA IN CHILDREN

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Children who have experienced one or more episodes of acute obstructive bronchitis are at high risk of developing bronchial asthma. ***Purpose of the study***. On the basis of clinical, laboratory and cytological data of induced sputum, obtained by dynamic observation of children at risk for the formation of asthma, develop an algorithm for early diagnosis of this disease. ***Methods:*** 54 children were under observation for 18 months. Inclusion criteria: 1 or more episodes of acute obstructive bronchitis in history, the age of children from 1 year to 5 years. All children at the beginning of the study and in the dynamics were examined, collecting history, the study of cytology of nasal secretions and induced sputum, determined the level of eosinophils of the complete blood count, the level of total IgE blood. ***Results***. During the observation period, 29 children did not manifest bronchial asthma (group 1), 25 children had bronchial asthma (group 2). At the time of the start of the study, in group 2 compared with group 1, there were more children with elevated levels of blood eosinophils, nasal secretions, total blood IgE, and sputum eosinophil levels ≥2.5% ($p<0.05$). The level of eosinophils induced sputum in children of the 2nd group was high 6.0% [2.4–17.0%], and at the time of the end of the study it was marked to increase 2 times 12.0% [4.0–22.0%] ($p= 0.02$). 48% of children in group 2 had asthma risk index. Based on the data obtained, an algorithm for early diagnosis of bronchial asthma was developed. The level of eosinophils induced sputum ≥5% can be recommended as an available and reproducible biomarker for early diagnosis of bronchial asthma in children, the probability of diagnosis is 96%. When the level of eosinophils induced sputum in the range of ≥2.5% to <5% and a positive asthma risk index in children, asthma is diagnosed in 70.4% of cases.

DYSREGULATORY MECHANISMS OF THE RELATIONSHIP BETWEEN THE HUMORAL AND CELLULAR IMMUNE RESPONSE IN PRIMARY AGAMMAGLOBULINEMIA

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Primary immunodeficiency is an ideal natural model for studying the possibilities of functioning of the immune system with a defect of one of its links. In this regard, the primary immunodeficiency of the humoral type, which allows to evaluate the potential of the cell-based system in the whole (Ballow M., et al., 2009; Sizyakina L.,Andreeva I., 2017), is very informative. The analysis of the examination results of patients with X-linked agammaglobulinemia (XLA) was carried out to reveal the features of the functioning of the T-cell component of the adaptive immune response in the conditions of genetic antibody disorder. 12 men at the age of 10–25 years were under the supervision. The disease debuted in all patients in the first year of life and bacterial infections of the respiratory tract became a clinical manifestation. The diagnosis was con-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

firmed by the detection of a genetic defect of btk and/or a characteristic family history. The results of immunological testing after the detection of XLA before the replacement therapy were analyzed. Expression of surface receptors and intracellular lymphocyte proteins were studied by flow cytometry. Healthy blood donors were examined as a comparison group. In patients with XLA an increase in the number of mature T-lymphocytes was revealed (91.40=2.5%, in the control 68.88=0.38%). The increase in the total pool of T-cells was mediated by increase of $CD8^+$effectors (40.80±3.44%, in the control of 21.88±0.33%) with the strengthening of their cytolytic resources ($CD8^+Gr^+$32.60±3.84, in control of 9.38±2.21%). Changes in $CD4^+$ T-cells are associated with a decrease in the peripheral circulation of part of naive $CD4^+CD45RA^+$ lymphocytes (12.6±5.3%, in the control 29.2±6.1%) and suppressor $CD4^+CD25^+FoxP3^+$Treg (0.40±0.01%, in the control 1.3±0.3%). Thus, the genetically determined absence of mature B-cells and complete antibody genesis contributes to the increase of quantitative and functional parameters of T-effectors of adaptive immunity with the involvement of immunoregulatory mechanisms which support their high potential.

CYTOKINE PROFILE SPECIFICS AMONG PATIENTS, SUFFERING FROM ALLERGIC RHINITIS AND COMORBID PATHOLOGY

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Introduction: In cases of allergic rhinitis, comorbid pathology determines inflammation process flow, as well as phenotype formation process and disease severeness. Adequate and timely inflammation monitoring among patients, suffering from allergic rhinitis, determines basic therapy effectiveness. Actual scientific data witness the fact, that cytokine profile evaluation among patients, suffering from various allergic rhinitis phenotypes is an effective allergic inflammation monitoring tool. ***Methods:*** Research method involved local and serum specific cytokines content (IL-2, IL-4, IL-8, IL-10, γINF, αTNF) evaluation, both in blood serum and nasal lavage, among 94 patients (no exacerbation), suffering from various perennial allergic rhinitis types. Cytokine content was determined using immunoenzymatic method among: 25 patients, suffering from allergic rhinitis, associated with herpetic-viral infection, 18 patients, suffering from allergic rhinitis and obesity, 21 patients, suffering from BA associated allergic rhinitis, 18 patients, suffering from vegetative dystonia-associated allergic rhinitis, 12 patients, suffering from local allergic rhinitis. ***Results:*** Serum cytokine status research, conducted among patients, suffering from perennial allergic rhinitis (no exacerbation), showed split-level IL-4 increase among 72% patients and nasal secret IL-4 level increase among all the patients. γINF serum level content change was stated only among patients, suffering from allergic rhinitis, associated with herpetic-viral infection. However, local γINF fraction witness split-level decrease among all the patients. Current changes can be evaluated as a typical allergic rhinitis cytokine profile. Speaking of IL-2, IL-8, IL-10, α-TNF serum fractions - there were no significant differences among patients, suffering from all the other allergic rhinitis phenotypes. However, reliable trends were stated in local fractions. Thus, key changes for patients, suffering from herpetic-viral infection, were IL- 8, αTNF and γINF production violation, in cases of obesity - IL- 8 and IL- 10 production violation, in cases of BA - IL-10 and γ INF production violation, in cases of vegetative dystonia - IL- 2 and IL- 8 production violation, in cases of local allergic rhinitis – IL- 8, IL-10, γINF production violation. Conclusions By virtue of acquired data, we can state local cytokine status changes specificity and serum cytokine profile parameters low informativeness among patients, suffering from various allergic rhinitis phenotypes. Local cytokine profile changes demonstrate inflammation specificity in cases of various allergic rhinitis phenotypes and should be recommended as allergic disease control markers.

CHRONIC ATYPICAL MIXED HERPESVIRUS INFECTION: ASSOCIATION WITH AUTOIMMUNE SYNDROME

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Introduction: Detection of various autoantibodies in the blood serum of patients suffering from atypical chronic active infection caused by herpes viruses (AH-HVI) is the cornerstone for the diagnosis of autoimmune pathology associated with the long-term course of the active viral process. Aim: to clarify the frequency of markers of autoimmune damage to the nervous system using screening study of autoantibodies in the serum of patients suffering from AH-HVI. ***Methods:*** Under our supervision were 18 people of both sexes aged 20 to 65 years suffering from mixed-AH-HVI. In complex study in addition to the traditional methods for the detection of herpes virus infections methods were used for serological diagnosis (EBV VCA IgM, EBV VCA IgG, CMV IgM, IgG CMV IgM, HSV1/2, IgG, HSV1/2), PCR method for detection of genome of viruses in biological material (blood, saliva, urine, scrapings from the tonsils and posterior pharyngeal wall). For detection of autoantibodies in the serum of patients used method is ELISA (Immunodot), Medipan GMBH, Germany Processing of results was performed using Microsoft Excel 2010. ***Results:*** In the blood serum of 90% of patients of the observed group we identified autoantibodies of different specificity. The dominant position among the detected antibodies was occupied by antiganglioside antibodies IgM and IgG in total (Anti-Gangliosid Dot), which were determined in the serum of 60% of patients. Among them, the first place was taken by autoantibodies to GM1 ganglioside, which were detected in blood samples in 80%of patients. On the second place on frequency of occurrence there were phosopholipid antibodies and ß2-glycoprotein (Anti-Phospholipid 10 Dot), including IgG to phosphatidycholine (45%). IgG antibodies to nuclear and cytoplasmic anti-

ISSN 1562-3629

gens (ANA 12 Line Dot) were found in 16.7% of patients with a predominant value to the DS DNA antigen. ***Conclusion:*** The obtained data indicate that the long-term course of AH-HVI is associated with the development of autoimmune syndrome, including neurological one. Detection of autoantibodies of different specificity, including to the nervous tissue, allows the detection of autoimmune process, to evaluate their activity and provides an affordable opportunity to monitor the effectiveness of the therapy.

NEUTROPHILIC GRANULOCYTES PHAGOCYTIC ACTIVITY AND DYNAMICS OF NEUTROPHIL EXTRACELLULAR NETWORKS FORMATION IN WOUND EXUDATES IN CHILDREN WITH SMALL PURULENT INFECTION

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Study of immune system in children with atypically proceeding small purulent infection (SPI) is actual problem. Today main antibacterial protection mechanisms of neutrophilic granulocytes (NG) include not only phagocytosis, but also NETosis. ***Aim*** To conduct comparative dynamic study of NG phagocytic function and its ability to form NETs on peripheral blood (PB) and purulent wound exudates in children with SPI.

In PB of 16 children (4–8 years old) with SPI and smears-prints (SP) evaluated NG phagocytic function and NET ability: before surgery-gr1; for 3 days-gr 2; on day 5-gr3 after surgery. Control-PB of 7 healthy children.

In PB NG of gr1 we revealed defect phagocytic function, leukocytes increase. In SP gr1 noted NG predominance, out of 100 NG–35,7[29,7;36,8]% were phagocytized, 15,5[10,7;22,4]% were destroyed, 26[18,7;29,3]% were inactive and 21,3[14,7;31,9]% with NET. In SP of gr1% PAN is 1,4 times lower than in PB–37,7[23,7;39,0] with reduced seizure, causing %D 66,1[62,3;66,3]. In SP of gr2 in 75% of cases were detected non-phagocytic NG due to absence of microbial background, in 18,8[7,9;33,5]% – NET; and in 25% of cases revealed low %PAN–11,1[10,4;12,9] with good seizure and digestion against high NET level–66,3[57,9;68,5]%. In PB of gr 3 were revealed decrease in leukocytes and NG phagocytic function, which indicates depletion of functional capabilities or inclusion of factors inhibiting the full-fledged work of NG. In SP gr3 in 40% of cases were detected eosinophils–41,2[37,9;43,5]%, isolated macrophages and NET–12,05[9,25;16,7]%, the absence of intact NG was noted. In gr 2 with initially high NET was noted its decline in 2,27 times on day 5.

Realization of NG bactericidal potential in children with SPI in focus of inflammation is carried out by phagocytosis and NETosis. Complex two-level study phagocytosis completion and NETosiss is necessary to verify NG defective functioning of local and systemic immunity with the detection of inflammation main markers.

PROBABILISTIC PROGNOSIS IN HUMAN COGNITIVE FUNCTIONS ON PROBLEMATIC SITUATIONS

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An informative assessment of probabilistic prognosis definition as an innovative estimation of human intelligence method to be interested for a wide range of scientific researches. The success of solving tasks in situations with varying probability of events and the structure of their relationship determines the human life quality and safety ultimately. As the basic research methodology was used a computer version of the new psychological original methodology “Prognosis 1, 2.5” developed for healthy adult subjects for integrative brain activity assessment. This approach is based on a commonly used in psychology method of "game of guessing.” It is based on testing subject to determine the different symbols orders in three different structure sets by predicting both and of symbols. The "Prognosis 2.5" method is widely used to assess of psychophysiological man status in different situations. The present research platform is based on the simultaneous registration of Parkinson disease EEG indices, transcranial dopplerogramm ("MultiDFop-P") at the base of the Middle cerebral artery, reoencefalogramm ("Mitsar), ECG and chest breathing movements on the PC of Windows XP by using the ADC" PowerLab-4 and brain predictive abilities assessment by computerized method of" Prognozis-2.5 " as our researches showed. *This survey was supported by “Bodiflo”, LLC (Australia) and ITAG (United States).*

ATOPIC DERMATITIS AND SKIN MICROBIOME

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Atopic dermatitis (AD) is a chronic inflammatory disease with the periodic exacerbation and remissions. Long term treatment with various kind of topical and systemic medications causes the subsequent side effects. And it’s very important to find the way how to treat AD by the low dose of topical corticosteroids and other medications. Emollients are a cornerstone for background therapy and a maintained treatment in atopic dermatitis. Especially those that can protect the normal flora of skin. The study was based on the view that the skin has the specific microbiome. They protect our body and is responsible for human physiology. Microbiome is forming at the the start of infant’s life, it depends on the way of delivery and also how is close the contact between infant and mother. Atopic dermatitis causes the change of microbiome. For healthy skin is characterized the higher grade of variety of micro flora then for atopic skin. The low grade of microbiomes is the marker for atopic dermatitis. For effectiveness of treatment is highly important the strength of skin barrier and normal microbiome of the skin. Therefore, for choosing of background therapy for atopic dermatitis we should prefer the moisturiz-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

ers which can regenerate of skin microbiome. Combination topical corticosteroids + emollients (which has possibility to regenerate of skin microbiome) promotes releasing of exacerbation and avoid patient for long term treatment with topical corticosteroids. To use this kind of moisturizers during the remission as a component of proactive therapy help us to prolong the remission. To identify which particular skin microbiome improving moisturizers should be used in each cases of AD is the main goal for future researches.

FAMILIAL BENIGN PEMPHIGUS (HAILEY-HAILEY DISEASE) - SUCCESSFULLY CONTROLLED BY DOXYCYCLINE

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Introduction: Familial benign pemphigus known as Hailey-Hailey Disease (HHD) is rare autosomal dominant genetic skin disease. It does not have nosological relation to pemphigus vulgaris and to autoimmunity. The suprabasilar acantholysis (epidermal blistering) is caused by genetically mediated primary defect in a calcium pump protein which causes disturbance of adhesion between keratinocytes. HHD clinically is characterized by inflammatory, weeping and macerated areas in the large folds of the body. Frequently family members are affected. HHD has a chronic nature and multiple recurrences, which make the disease bothersome for patients and a treatment challenge for physicians. Multiple treatment modalities are often needed to obtain benefit. The best evidence exists that refractory HHD has shown the most benefit with oral antibiotics, in line with topical steroids and antimicrobials. ***Case presentation***: We are presenting an interesting clinical case, when the treatment of complications of basic therapy familial benign chronic pemphigus led to an improvement the symptoms of previously uncontrolled disease. A 49 year old female patient was admitted to our clinic with erythema, papules, pustules on her cheeks, chin and around the nostrils, associated with dry skin, scaling, itching, and Cushingoid appearance. Typical clinical signs of Hailey Hailey Disease – eroded plaques in the genital area, armpits, groin and anus with overlying crusts were identified. Patients' mother, sister and daughter were affected with the same symptoms, of various intensity. The diagnosis of HHD was confirmed histologically. Patient received oral methylprednisolone for 3 years (initial doses 48 mg, with subsequently decrease up to 12 mg) and when presented to us had a not controlled recalcitrant disease. Under therapy she developed papulopustular rash on the face, and started use of clobetasol ointment for 3 months on her own decision, which led to the deterioration of the facial rash. The diagnosis steroid rosacea was stated, significant increase in number of demodex mites was identified by direct microscopy of eyelash and facial scrap. Treatment with a systemic steroid has been discontinued, the patient applied combined cream containing betamethasone and antimicrobial agents on the affected folds, topical 0.75% metronidazole cream on the face, in combination with oral doxycycline at a dose of 100 mg 2 times a day, followed by reduction of the dose to 50 mg for 6 week. The therapy quickly stopped the rash on the face (after 3 weeks) and gave good control of the underlying disease. After 10 week the signs of Cushingoid were significantly reduced. ***Conclusuon:*** The therapy of HHD is challenging, multiple treatment modalities are often needed to obtain benefit. We achieved clinical improvement under doxycycline treatment in a HHD patient as for steroid induced rosacea, as well as for before uncontrolled underlying disease. Long lasted steroid treatment in patients with Hailey- Hailey disease can be successfully replaced with doxycycline in combination with local steroids and antimicrobials.

THOMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND MODERN APPROACH TO ITS INVESTIGATION AND TREATMENT

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Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet rich-thrombi. TTP is specifically related to a severe deficiency in ADAMTS13 (a disintegrin and metalloprotease with thrombospomdin type 1 repeats, member 13), the specific von Willebrand factor-cleaving protease. ADAMTS13 deficiency is most frequently acquired via ADAMTS13 autoantibodies, but rarely, it is inherited via mutations of the ADAMTS13 gane. The first acute episode of TTP usually occurs during adulthood, with a predominant anti – ADAMTS13 autoimmune etiology. In rare cases, however, TTP begins as soon as childhood, with frequent inherited forms. TTP is 2 – fold more frequent in women and its outcome is characterized by a relapsing tendency. In addition to the microangiopathic hemolytic anemia and consumption thrombocytopenia, classical parameters for hemolysis show a high reticulocyte count ($>120\times10^9$/l), an undetectable serum haptoglobin concentration, and an elevated lactate dehybrogenase level, a marker for tissue damage. the fresence of schistocytes on the blood smear (helmet cells; small, irregular triangular, or crescent –shaped cells; pointed projections; and lack of central pallor) with a confident threshold value of 1% is the morphologic hallmark of the disease. Except in some associated autoimmune contexts (SLE), the erythrocyte Coombs' test is negative, Standard coagulation parameters are usually normal. Renal testing may show proteinuria, hematuria, and sometimes increased plasma urea and creatinine levels. An increased cardiac troponin level (>0.1 μg/L) is present in up to 60% of cases, the majority of whom have no clinical cardiac involvement. Electrocardiogram changes, mainly repolarization disorders, are present in 10% of cases. Point-based TTP prediction scores have been validated to predict an acquired ADAMTS13 deficiency. These

ISSN 1562-3629

scores include platelet count, serum creatinine level, and either detectable antinuclear antibodies 50 or d-dimer, reticulocytes, and indirect bilirubin.

Clinical spectrum of TTP Today, the historical clinical pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal insufficiency that used to define TTP appears obsolete, as several cohort studies have clearly demonstrated that these 5 symptoms were present in less than 10% of patients with an acute TTP. Rapid recognition of TTP is crucial to initiate appropriate treatment. The first-line therapy for acute TTP is based on daily tharapeutic plasma exchange supplying deficient ADAMTS13, with or without steroids. Additional immune modulators targeting ADAMTS13 autoantibodies are mainly based on steroids and humanized anti–CD20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive tharapies including twice-daily plasma exchange; pulses of cyclophosphamide, vincristine, or cyclosporine A; Or salvage splenectomy are considered. New drugs including N-acetylcysteine, bortezomib, recombinant ADAMTS13, and caplacizumab show promise in the management of TTP.

FEATURES OF THE CLINICAL PICTURE OF INFECTION CAUSED BY THE HERPESVIRUS TYPE 6, IN CHILDREN WITH DIFFERENT VIRAL LOAD

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Introduction: The herpesvirus type 6 is a common herpetic infection, accompanied by fever, lymphadenopathy, arthralgia, ephemeral rash and sometimes complicated by the pneumonic process. The aim of the study was to determine the relationship between the clinical and laboratory picture of the infectious process and the magnitude of the viral load of VG-6. ***Materials and methods:*** A retrospective analysis of the data of 100 children was carried out in which the viral load of VG-6 was quantitatively determined by PCR. ***Results:*** fever (65%), the background of which was caused by catarrhal syndrome, less often – febrile convulsions, became the most frequent syndromes that occur with HH-6 infection; regional lymphadenopathy (38%), rash (29%) – vesicular in the oral cavity and generalized spotted-papular; articular syndrome (18%). The most common infection was the respiratory tract and ENT organs in the form of acute tonsillitis (13%), rhinopharyngitis (13%), pneumonia (9%) and bronchitis (11%). We first studied the features of the infectious disease clinic depending on the viral load of VG-6 (minimal – 100, maximum – 73600 copies / ml) and concluded that there is a connection between the viral load and some clinical and laboratory indicators. There was no correlation between some parameters (fever, articular syndrome, exanthema, leukocytosis) and viral load, except for the frequency of occurrence of weakened breathing and the neutrophil count. In 57% of cases, VG-6 was isolated along with other viruses: HSV 1-2 types, CMV, EBV, enteroviruses. Analysis of the severity of the clinical picture in children with mono-infection of VG-6 and with the virus-viral association showed no significant differences. ***Conclusions.*** 1. Clinical pictures VG-6 type is associated with the defeat of various organs and systems. 2. In 57% of children, the virus was a part of virus-virus associations, the presence of which did not aggravate the clinical course of VH-6 infection. 3. There is a direct correlation between the magnitude of the viral load of VG-6 and the degree of lesion of the respiratory system, the severity of neutrophilia.

CLINICAL AND DOPLEROGRAFIC CRITERIA FOR THE EFFECTIVENESS OF SUBLINGUAL ALLERGEN-SPECIFIC IMMUNOTHERAPY WITH A STANDARDIZED EXTRACT OF BIRCH POLLEN IN POLLINOSIS

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Introduction: The wide spread of allergic diseases associated with sensitization to pollen of trees dictates the need to choose the effective methods for treating pollen. At the moment, in addition to assessing the clinical effectiveness of therapy, there is the possibility of using functional methods, one of which is the dopplerographic examination of the blood flow velocity of the salivary glands. Concerning this, the aim of the study was to research the clinical efficacy of the sublingual allergen specific therapy (slASIT) with a standardized extract of birch pollen, in comparison with the dopplerographic evaluation of the blood flow velocity rate of the salivary glands

Methods: We've observed 124 patients, who have sensitization to pollen of plants and clinical forms of respiratory allergy with clinical manifestations in the birch blossom season. Group 1 – 66 people receiving a standardized extract of birch pollen, second group of 58 people without ASIT receiving standard nosotropic therapy.

Results: All observed patients reported sensitization to birch pollen, 1/3 of them had a cross allergy. After 1 course of therapy in 88% of cases, a marked decrease in allergy symptoms during the pollination season was noted. Doppler study in patients with sublingual allergen specific therapy showed a significant increase in the blood flow velocity of the sublingual salivary gland. Comparative analysis showed that patients who was receiving only nosotropic therapy did not have complete relief of the symptoms of pollinosis, and a doplerogram study of the bloodstream of the sublingual salivary gland did not reveal an increase in blood flow.

Conclusions: The sublingual mode of introduction ASIT with a standardized extract of birch pollen is effective and preferable than only pathogenetic therapy. A criterion for the effectiveness of the sublingual allergen of a specific therapy with a standardized birch pollen extract can be an available method-doplerografic study of the bloodstream of the sublingual salivary gland.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

THE METABOLIC CORRECTION OF THE EXPERIMENTAL ALLERGIC REACTION IN ACCORDANCE WITH THE IMMEDIATE HYPERSENSITIVITY

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For allergic reactions along with the classic immunological manifestations the metabolic disorders are characteristic including the development of oxidative stress. In this association, the study in possible usage of remedies of the antioxidant orientation is urgent for correction of immune and oxidative disorders. The study has been performed on 75 white rats. The control group has been composed of the intact animals. The animals of the 2–5 groups have undergone the intraperitoneal immunization by means of ovalbumin. The rats of the 2 group have not been corrected (the comparison group). The animals of the 3–5 groups have received sodium dichloroacetate (DCA, the 3 group) for a month before and during the entire experiment as well as the probiotics with the antioxidant compound (BAS, EAN: 5907529461563, the 4 group) or the water with decreased content of deuterium (DDW, 43 ppm, the 5 group). The development of the experimental immediate hypersensitivity in animals of the 2 and the 4 groups has been accompanied by the increase in production of the general IgE by 6 times (33,6 MU/ml) as well as the imbalance of cytokines including the prevalence of the Th2-cytokine profile (IL4, IL10) and the decrease in activity of the Th1-lymphocytes (IFNγ, IL2). The IgE content in animals of the 3 group has been higher than the control indices by 46% (6.26 MU/ml) while in the 5 group it has possessed no significant differences. In animals of the 3 and the 5 groups the cytokine balance of Th1/Th2 has been shifted to the Th1 which has been associated with the increase in IL4 (by 5-6 times) in comparison with the 2 group. Besides the level of Th1 cytokines has increased due to the IFNγ level higher than the control values by 17-23 times; the IL2 production has also increased (by 3–6 times). In rats of the 4 group the significant increase in activity of catalase, glutathione peroxidase and glutathione reductase by 20–50% in comparison with the control values. Thus, the researched BAS has proved its antioxidant properties while it had no positive influence upon the cytokine and immunoglobulin profiles. This fact is of great importance to the prospects of the correction of the immunological disorders by allergic reactions by means of the immunomodulators of pathogenetic action.

IMPACT OF ENDURANCE TRAINING BY ELITE ATHLETES ON IMMUNE CELL SUBPOPULATIONS AND VITRO SECRETION OF IMMUNOREGULATORY CYTOKINES

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Background: Prolonged strenuous endurance exercise may impact cytokine production by PBMC which leads to immune dysregulation. The influence of different types of sports (bobsled, biathlon and bullet shooting) on immune cell subpopulations and pro- and anti-inflammatory cytokine synthesis was assessed. ***Methods:*** 153 elite athletes of both sexes specializing in bobsled, biathlon and bullet shooting were examined. Studies were conducted on athletes in the pre-competition period of sports training. The main subpopulations of mononuclear cells in peripheral blood (PBMC) were assessed by flow cytometry (FC-500, Beckman Coulter, USA). Cytokine concentrations (IL4, IL 6, IL 10, IL 18 and IFNγ) were assayed by ELISA. ***Results:*** Among PBMC subpopulations, endurance exercises impacted the number of NKT and activated T cells with NKT cell numbers greater in male bobsledders versus bullet shooting and biathlon (42.4% and 44.3%, respectively). The number of activated T cells (CD25+) was greater in bullet shooting and bobsleigh athletes versus the biathlon group (34.9% and 22.7%, respectively). In female athletes the number of CD25+ cells in the shooting and bobsled groups was greater by 46.1% and 25.5%, respectively versus the biathlon group ($p<0.05$). Increased IL-10 occurred in bobsleds in comparison to bullet shooting and biathlon: 32% and 80% in male and 70.5% and 83% in female, respectively ($p<0.05$). The concentration of IL-18 in male bobsledders and biathlon was 30% and 34% gvreater, respectively, compared with bullet shooting ($p <0.05$). Serum concentrations of IFNγ in male as well as female athletes showed an increase of 41.6% and 39.5%, respectively versus biathletes ($p<0.05$). Increased IL-4 occurred in the male biathlon group by 39.7% and 13%, respectively, versus the bullet shooting and bobsleigh athletes ($p<0.05$). IL-6 was increased in the male biathlon group, compared to bullet shooting and bobsledders by 76.7% and 70.3%, respectively ($p<0.05$). ***Conclusions:*** Prolonged endurance exercises impacts secretion of pro- and anti-inflammatory cytokines in athletes of different sport specializations. Concentrations of studied cytokines did not exceed reference values perhaps due to specialized sport nutrition, which may restore immune function.

AUTOANTIBODIES TO INTERORGANIC THERMOSTABLE ANTIGENS – PARTICIPANTS IN THE PATHOLOGICAL OR PHYSIOLOGICAL PROCESS?

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Introduction: With the development of personalized medicine, special attention is paid to searching not only genetic, but also metabolic markers of early signs of pathological changes. These include a multicomponent assessment of the level of autoantibodies in a preventive or diagnostic examination study (AB Poletaev, LP Churilov, I. R. Cohen, M. Harel, Y. Shoenfeld). However, up to the present time there is no consensus on the mechanism of formation and the functional signi-

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ficance of autoantibodies, except for those that play a key role in the development of autoimmune diseases. In the 1970s N. Jerne substantiated the synthesis of regulatory autoantibodies to his own antigens in a healthy organism, and P. Grabar suggested that normal autoantibodies can be carriers of cell catabolism products. According to A.D. Ado, permanent autoimmune processes in a healthy body and autoimmune disorders in diseases are not identical. As a result of the research, many autoantibodies with a physiological function were detected. Aim: To search for autoantibodies in the blood serum to tissue interorganic thermostable antigens (TI1 and TI2). ***Objects of research:*** TI1 and TI2 were identified as individual antigens in the 90s of the 20th century and later studied as markers of destructive processes (D.M. Nikulina, V.V. Belopasov, O.V. Petrova and others). The search for autoantibodies was carried out in the blood serum of healthy persons individuals, pregnant women and patients with kidney diseases. ***Results:*** First, fractionation of the proteins of the kidney extract under different temperature regimes was performed. Fractions after exposure to 80°C and 100 were used for immunization of rabbits to obtain antiserum. Immunodiffusion and immunoelectrophoresis methods in these fractions revealed three precipitation lines, one of which was identified as ferritin. Two other components were used as test antigens, for to which antibodies were detected in serum samples of pregnant women with late gestation and patients with glomerulonephritis. The frequency of detection depended on the presence of complications severity of pregnancy and on the severity of kidney disease. ***Conclusion:*** Given the presence of TI1 and TI2 in all tissues of the body, it can be assumed that antibodies to them are taking part in elimination the decay products of cellular elements in apoptosis. We believe that in this case, the quantitative production of normal autoantibodies is enhanced, in contrast to qualitative changes in the development of autoimmune diseases. It can also be assumed that the synthesis of these autoantibodies will be intensified in the old age with a predominance of catabolic processes in all tissues.

ASSOCIATION OF TLR9 EXPRESSION WITH COMPLICATIONS AFTER ALLOGENEIC KIDNEY TRANSPLANTATION

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Great progress has been achieved over the last years in allogeneic transplantation of kidneys. However, postoperative complications, associated with inflammatory reactions and leading to graft dysfunction, occur in a number of cases (up to 20%) after transplantation. It is known that activation of inflammatory reactions is mediated by innate immunity receptors, particularly TLRs, which are capable of recognizing self-molecules (DAMPs). TLR9 can recognize a DNA released from damaged cells during transplantation. Change of TLR9 expression is a possible cause of inflammatory overreaction in renal graft. The purpose of this research was to evaluate the dynamics of the TLR9 gene expression level in mononuclear blood cells of patients who underwent allogeneic kidney transplantation. Functional activity of blood mononuclear cells (PBMCs) was studied from patients divided into two groups: first consists of 11 patients with renal graft, 9 to 16 years old, second (control) consists of 7 donors (RCCH, kidney transplantation ward, Molchanova E.A.). PBMCs isolation was done by A. Boyum sedimentation method, with further TLR9 gene expression dynamics analyzing in 1,14,24,48 hours after incubation. Then, RNA was extracted (*RIBO-sorb*, Amplisens, Russia) from PBMCs and used in reverse transcription (*OT-1*,Syntol, Russia), then analyzed in qPCR (*PCR-Mix*, Syntol, Russia), with DT-96 PCR system (R&P DNA-Technology, Russia). TLR9 expression was evaluated relative to the cells quantity. Statistical analysis was performed using Microsoft Excel. There was a slight increase of TLR9 gene expression from 14 to 48 hours of incubation in control group. 50% of patients who underwent transplantation in the last 10 months showed twofold increase of TLR9 gene expression after 1 hour of incubation. In patients who underwent transplantation more than 2 years ago, the receptor gene expression dynamics decreased 4 to 10 times comparing to initial values. It should be noted that initial values of TLR9 expression in patients with repeated kidney transplantation were higher than in control group. Thus, high level of TLR9 gene expression in patients with repeated transplantation may indicate the role of this receptor in graft damage initiation, making TLR9 a possible marker of renal graft complications.

ROLE OF HUMIC SUBSTANCES IN THE HYGIENE HYPOTHESIS FOR AUTOIMMUNE AND ALLERGIC DISEASES

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Background: The hygiene hypothesis for autoimmune and allergic diseases, which exists nowadays, shows that human immune system is dependent on various environment factors. We consider the effects of humic substances (HS) to be important in understanding the hygiene hypothesis, since HS account for up to 35% of the soil. ***Methods:*** We studied the following fractions of HS: humic (HA), hymatomelanic (HMA), fulvic (FA) and humic-fulvic acids (HFA). Study of immunotropic properties: change of IgE-antibody levels as a response to HS injection, and propagation of anaphylactic reaction in mice as a response to HS injection. Studies of all immunotropic properties were conducted using highly allergenic ovalbumin (OVA) solution in doses of 1 mg/kg, and HS solutions in doses of 2.5 mg/kg and 25 mg/kg. Change of IgE-antibody levels as a response to HS injection was studied, employing 6 groups of mice: 1st group (reference) – mice were injected OVA, but not injected HS; 2nd and 3rd groups – mice were injected OVA, and were injected HS solutions once: 5 days before the first immunization with OVA (estimate of prophylactic effect of HS); 4th and 5th groups – mice were injected OVA, and were injected HS solutions once: 5 days before the second immunization with OVA (estimate of influence of HS on developing IgE-response); 6th group (negative reference group) – mice were injected PBS solution. Propagation of anaphylactic reac-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

tion in mice as a response to HS injection was studied, employing 4 groups of mice: 1st group (reference) – mice were injected PBS solution once; 2nd and 3rd groups – mice were injected HS solutions once; 4th group – mice were injected OVA solution once. Two weeks later, a resolving (x3) dose of sensibilizer was injected to each group of animals. ***Results and Conclusions:*** Change of IgE-antibody levels as a response to HS injection showed that the investigated solutions of HS inhibit the development of allergies. IgE-antibody levels in serum of mice: 1st group – 0,45±0,04; 2nd and 3rd groups – 0,17±0,04 and 0,29±0,05; 4th and 5th groups – 0,41±0,04 и 0,35±0,04; 6th group – 0±0,01. Propagation of anaphylactic reaction in mice as a response to HS injection was assessed by the Rupa and Mine index: 1st group was 0/4; 2nd and 3rd group – 0/4; 4th group is 4/4. On the basis of the foregoing, it can be safely stated that HS possess immunotropic and affect the development of allergies.

FUNCTIONAL REGIMES OF PLASMACYTOID DENDRITIC CELLS, FORMED UPON EXPOSURE TO CPG-ODN OF VARIOUS CLASSES

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Plasmacytoid dendritic cells (pDC) is a population of dendritic cells characterized by the synthesis of IFN-I and the ability to represent antigens to T cells. pDC are the main producers of IFN-I, providing immune protection against viral infections. Also, pDC is able to function as an antigen presenting cells (APC), while mediating both activation of the secondary immune response, so suppression of dangerous immune responses by induction of regulatory T cells (Treg). pDCs contribute to the development of a humoral immune response by regulating the functions of B-lymphocytes (mediating their differentiation into plasmocytes and switching the synthesis of immunoglobulins to IgG), but they can also promote the development of Th1 and Th17 types associated with the cellular immune response. The pleotropic functions of pDC provide the basis for an active study of this population, its role in pathology and possible therapeutic manipulations with pDC in the treatment of various diseases. In this study, different types of functional activity of plasmacytoid dendritic cells, formed upon exposure to CpG-ODN of various classes, are considered.

CADAVERINE AS A REGULATOR OF PRO- AND EUKARYOTIC CELL ACTIVITY

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Cadaverin widely circulated in nature. It has an impact on all the components of any biotope of the human body. It was shown that cadaverin can be synthesized as cells of the human body, and microorganisms. We can assume that cadaverin is a universal regulator activity of cells different origin. Aim of the study was to assess the impact of cadaverina on functional activity of eukaryotic cells and microorganisms. ***Methods***. Been evaluated by phagocytic activity peripheral blood leukocytes almost healthy donors at the method Shilov et al. (2003) after prior incubation of cells with cadaverinom (0.01 M) within 60 minutes at 37°C. *Escherichia coli* K12 was cultivated in the LB-broth and it was determined the contents of cadaverina by liquid chromatography. ***Results:*** It was shown that cadaverin has the ability to reduce phagocytic activity of peripheral blood leukocytes, changes the ratio of phagocytic cells. In the first place is reduced the number of phagocytic neutrophils (48%). However, among phagocytic cells increases the number of those are captured more than 2 objects. Marked increase absorption ability of eosinophils that requires more detailed study. On the other hand, it was established that the synthesis of cadaverin by *E. coli* strictly depends on the content of oxygen in the environment. When the cultivation was aerobic in terms of the content of cadaverin in the environment was significantly decreased. Under reduction of aeration cadaverin contents were grown in more than 10 times. We can assume that in phagosome E. coli, while in terms of the lack of oxygen and increase of radicals contents, increases the cadaverin synthesis, which allows the microorganism to survive in adverse conditions, because cadaverin inhibits phagocytic activity of leukocytes and stands in the role of the antioxidant. ***Conclusion:*** Thus, cadaverin can contribute to the survival *E. coli* in conditions with reduction of aeration that are created in phagosome. At the same time, cadaverin inhibits functional activity of phagocytic cells, giving additional opportunities for *E. coli* growth.

EXPERIMENTAL REMODELING IN VITRO OF THE TRANSFORMED SUBPOPULATION IFNA/BR1$^+$CD119$^+$TLR4$^+$ NEUTROPHILIC GRANULOCYTES IN CHRONIC HERPESVIRUS INFECTION

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Neutrophilic granulocytes (NGs) are multipotent cells of the immune system, which participate in antiviral protection. It is known that in cases of chronic herpes-viral infections (CHVI), neutropenia, disturbances of the interferon system are often observed. This is the reason, why we are interested in studying the features of the phenotype of the IFNa/βR1$^+$CD119$^+$TLR4$^+$NGs subpopulation in CHVI and the possibilities of its remodeling under the influence of the regulatory hexapeptide (HP) – arginyl-α-aspartyl-lysyl-valyl-tyrosyl-arginine. We conducted an experimental study in the system *in vitro* on 99 peripheral blood samples obtained from 21 patients with CHVI and from 15 conditionally healthy individuals

ISSN 1562-3629

(control group), both sexes, aged 23 to 60 years. To detect herpes viruses, the sero- and PCR diagnostics methods were used. The phenotype of IFNa/βR1$^+$CD119$^+$TLR4$^+$NGs subpopulation was studied by flow cytometry. It was established that the number of IFNα/βR1$^+$NGs, CD119$^+$NGs in persons with CHVI was significantly higher than in conditionally healthy individuals. The number of NGs bearing TLR4 molecules on the membrane in CHVI was different in ways: in one group of patients a decrease in the number of TLR4$^+$NGs was observed, and in the other group there was an increase in the number of TLR4$^+$NGs compared to the control group. It was shown that after incubation of NGs of patients with CHVI with HP at the final concentration of 10-6 mg/ml, for 1 hour at 37°C, the percent of NGs expressing the IFNα/βR1 and CD119 receptors was increased; the number of TLR4$^+$NGs in the group with higher number of them was decreased, while in the group with low number of TLR4$^+$NGs – did not change; the expression density of IFNα/βR1 molecules on the NG membrane was increased in group'patients with CHVI, while the expression density of CD119 receptor was decreased, which approached the level of control. In conclusion, it should be noted that patients with CHVI have a certain negative transformation of the phenotype of the IFNα/βR1$^+$IFNγR$^+$TLR4$^+$NGs subpopulation. HP, which is a synthetic analogue of the active center of the thymus hormone – thymopoietin, has modulating properties, – positively remodulated the transformed phenotype in CHVI of the IFNα/βR1$^+$IFNγR$^+$TLR4$^+$NGs subpopulation.

THE DIFFERENTIATED EFFECTS OF RECOMBINANT IFNA2B ON THE MEMBRANE EXPRESSION OF CD16, CD66B, CD33, CD11B OF NON-TRANSFORMED AND EXPERIMENTALLY TRANSFORMED IN VITRO NEUTROPHILIC GRANULOCYTES OF HEALTHY CHILDREN

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Neutrophilic granulocytes (NG) have a dominant role in both the start and subsequent regulation and realization of the immune response. There are populations and subpopulations of NG, which differ in the relief of membrane antigens, which predetermines the functional orientation of the cell. The aim of the study was to study the effect of recombinant IFNα2b (rIFNα2b) on the non-transformed and *in vitro* transformed phenotype of CD16$^+$CD66b$^+$CD33$^+$CD11b$^+$NG of healthy children. Materials and methods. 80 blood samples of 10 children 3–5 years old were examined. Immunophenotyping was performed: %NG, carrying CD16, CD66b, CD33, CD11b receptors; the intensity of fluorescence (MFI). These parameters of untransformed NG (control) and NG after the incubation with rIFNα2b and fMLP were evaluated in vitro experiment. Results. Analysis of the results of the study revealed that 97.03[94.31, 98.40]% of the control NG are represented by a subpopulation of CD16$^+$CD66b$^+$CD33$^+$CD11b$^+$ with different equipment according to MFI. We found a high MFI of CD16 – 139[115,3;152,3], a low MFI of CD66b was 4,6[4,2;5,0], and MFI of CD33 was 3,7[3,3;4,6] and the average MFI CD11b was 18,3[15,8;21,0]. Under the influence of fMLP, the transformation of this phenotype was revealed: a significant increase in MFI CD66b (2.5-fold), MFI CD11b (1,9-fold), MFI CD16 (1,4-fold), which indicated adequate inclusion of healthy children in response on the bacterial antigen. Exposure with rIFNα2b had a multidirectional effect on the expression of the receptors: an increase in MFI CD66b (1,5-fold) and a decrease in MFI CD11b (1,4-fold), no effect on MFI CD33 and CD16., it was found that the expression levels of the studied receptors were increased in comparison with the control values ($p<0,05$) with the combined effects of fMLP and rIFNα2β, but did not differ significantly from the activated profile of the NG under the influence of fMLP, except for the CD66b receptor, which was higher when mono- influences of both fMLP 11,4[10,8;12,8] and rIFNα2b 7,05[5,63;8,14] ($p <0.05$). Conclusion. The regulatory effect of rIFNα2β on the nontransformed phenotype of CD16$^+$CD66b$^+$CD33$^+$CD11b$^+$NG subpopulation and modulating effects on in vitro transformed phenotype of NG was revealed, which facilitated the remodeling of the proinflammatory phenotype of NG in anti-inflammatory.

NEGATIVELY TRANSFORMED PHENOTYPE OF NEUTROPHILIC GRANULOCYTES CD64$^-$CD32$^-$CD16$^+$CD11B$^+$: BIOMARKER OF "SMALL PURULENT INFECTION" IN CHILDREN

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The existence of subpopulations of neutrophilic granulocytes (NG) with different ability to regulate or suppress cells of innate and adaptive immunity producing a spectrum of pro, anti-inflammatory and regulatory cytokines is proved. Earlier it was shown that in severe bacterial infections a subpopulation of CD64$^+$CD32$^+$CD16$^+$CD11b$^+$NG increases in newborns peripheral blood (PB). But the phenotypic changes of this subpopulation in children with purulent lymphadenitis and abscesses of soft tissues – small purulent infection (SPI) – are poorly understood. The purpose of the study: clarification of the phenotypes of the subpopulation of NG in PB, expressing CD64, CD16, CD32, CD11b, in healthy children and in children with SPI. ***Methods:*** Flow cytometry was used to evaluate: % NG, carrying CD64, CD16, CD32, CD11b, their expression density (MFI) in children 4–5 years in 20 PB samples with SPI on day 2-3 of acute purulent process and in 17 PB samples healthy children. ***Results:*** It was found that in healthy children a major subpopulation of NG with a phenotype CD64-CD32$^+$CD16$^+$CD11b$^+$ – 90,24%[89,9;96,8] and 2 minor subpopulations with phenotypes: CD64$^+$CD32$^+$CD16$^+$CD11b$^+$ - 2,94%[2,15;3,54] and CD64$^-$CD32$^-$CD16$^+$CD11b$^+$ – 0,52% [0;1,3]. At SPI, the major subpopulation of NG decreased by 1,5 times - 61,66%[59,7;76,8], CD64$^-$CD32$^-$CD16$^+$CD11b$^+$NG increased significantly (by 15 times) to 33,15%[24,45;41,85] and CD64$^+$CD32$^+$CD16$^+$CD11b$^+$NG increased by 3,5 times - 2,1%[1,57;4,05]. In patients with SPI in the major subpopulation MFI CD11b was 3 5 times higher ($p <0$ 05) and MFI CD32, MFI CD16 did not differ from the control. The appearance of CD64$^-$CD32$^-$CD16$^+$CD11b$^+$NG subpopulation in SPI with no expression of CD64 and CD32 receptors which necessary

International Journal on Immunorehabilitation
2019 Volume 21 No 1

for the full realization of phagocytic function is an unfavorable factor. The absence of CD32 may be associated with a congenital defect, blocking of expression, or shedding, while MFI CD11b increases to 8 times compensatory. Minor subpopulation of $CD64^+CD32^+CD16^+CD11b^+$NG was characterized by high equipment of CD16 and CD11b (3 times higher than control, p <0 05). ***Conclusion***: A significant increase in the subpopulation of NG with a negatively transformed $CD64^+CD32^+CD16^+CD11b^+$ is a prognostically unfavorable factor. Lack of adequate increase of NG with CD64 and defect of CD32 expression is the reason of inadequate inclusion of NG in the implementation of inflammation processes, which contributes to the emergence of SPI in children.

MOLECULAR FACTORS OF INNATE IMMUNITY IN THE REGULATION OF NEUROENDOCRINE AND IMMUNE REACTIONS UNDER THE STRESS CONDITION

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The role of molecular factors of innate immunity (human lactoferrin and rat defensins) was studied during the stress reaction. Rat defensins were isolated from rat exudate leukocytes by extraction, solid phase extraction and HPLC. Human lactoferrin was obtained from milk by degreasing, precipitation of casein, ion exchange chromatography and dialysis. As an experimental model, we used emotional-physical stress-swimming in cold water. Experiments were carried out on male Wistar rats. The test substances were injected intraperitoneally, in an amount of 100 μg/kg on animal weight for defensins, and 200 μg/kg for lactoferrin. The administration of antimicrobial proteins and peptides prevented the stress-induced increase in the level of the hormone-corticosterone (in 30 minutes after the stress). According to the literature, corticostatic activity was previously shown for some α-defensins. In the present study, the corticostatic activity was demonstrated for RNP-3 – peptide, that did not show this activity in *in vitro* testing. The corticoststic activity of lactoferrin was shown in this study for the first time. The involvement of defensins in the regulation of the level of corticosterone has been also proved by immunoneutralization reaction– an administration of anti- RNP3 antibodies before stress application, which led to the abolition of natural reduction of the hormone level at a period of 3 hours after stress. Under the conditions of this experiment, a normalizing effect of defensins and lactoferrin on stress-induced blood leukocyte changes was also shown. In addition, both, defensins and lactoferrin reduced stress-induced increase of gene expression of the anti-inflammatory cytokine IL-4, as well as the pattern-recognition receptor-TLR-4 in the spleen. The aggregate of data demonstrated the important role of antimicrobial proteins and peptides in the regulation of neuroimmune interactions.

REFERENCE VALUES OF STAT AND SOCS PROTEINS IN PATIENTS WITH METABOLIC SYNDROME

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Metabolic syndrome development is associated with inflammatory changes in tissues, meanwhile the proteins of intracellular signal transduction system are also important there [1–2]. It has been shown that such the systems are evolutionarily ancient and universal for humans and animals of different organization level. Variability of adipose tissue quantity correlates with the JAK/STAT systems activation. SOCS system proteins have their influence on insulin resistance (especially role of SOCS-1 and SOCS-3 is crucial for insulin effects inhibition) [4–5]. The evaluation of reference values is provided by ELISA (regarding concentration of transcription factors STAT1, STAT3, STAT6 and negative regulators SOCS 1, SOCS 3, SOCS 6 in the peripheral blood of patients with metabolic sindrome) to form a base for usage of the proteins as predictors of metabolic syndrome. 23 samples are studied (different sex and age). The mean levels for the proteins were: STAT1 0.46 ng/ml, STAT3 0.46 ng/ml, STAT6 0.52 ng/ml; SOCS1 0.22 ng/ml, SOCS3 0.76 ng/ml, SOCS6 0.30 ng/ml.

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COMPARATIVE CHARACTERISTICS OF DIAGNOSTIC METHODS OF ELISA AND PCR IN VERIFYING THE ACTIVITY OF TYPE 4 HERPES

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Introduction: The relevance of the study of herpes infections is preserved at the present stage, due to the widespread distribution among the world's population. The most controversial issue of herpetology is the diagnosis and identification of markers of chronic herpetic infections. The most widely used in modern laboratory diagnostics are methods of ELISA and PCR. The issue for discussion is the substrate in which the infectious agent and / or specific antibodies should determine. ***Purpose of the study:*** To perform a comparative analysis of ELISA and PCR in the verification of type 4 herpes. ***Methods:*** The material for the study was venous blood, urine, as well as the contents of the mucous membranes of the nose, throat (for all types of research were received voluntary informed consent of the parents) from 320 children in the age range from 9 months to 17 years. ***Results:*** ELISA revealed 100% of cases of contamination with EB virus. In 67% of the children, the markers of activation of the infectious process were determined. In the blood test using the PCR method, negative results were obtained. Positive reactions from 3 biological objects were 36 children (11.25%), in 62 positive reactions PCR were from the throat and nose - 19.38%, 43 children were diagnosed with a positive result only from the throat (13.44%), and 71 the child had positive PCR values from the nasal mucosa (22.19%). Only 51 children (15.94%) had positive values in the urine. The remaining children (in the number of 57) had a negative result of PCR studies from biological media. Children with neoplastic processes, prolonged subfebrile condition, leukemia reaction, lymphadenopathy had signs of chronic infection activation, a sharp increase in $CD95^+$ cells, positive markers for the presence and exacerbation of EBV in ELISA and PCR studies. ***Conclusion:*** The conducted studies clearly demonstrate the advantages of IFA blood, as a screening study, in the diagnosis of the staging of an infectious disease. It should be noted that, as the only ELISA method, it can not pretend to be diagnosed in herpetology. Only in combination with PCR, the diagnosis of infectious diseases becomes evident.

EPSTEIN-BARR VIRUS DNA IN HUMAN BIOLOGICAL MATERIALS AS A MARKER OF ACTIVITY OF VIRAL PROCESS IN ATYPICAL CHRONIC ACTIVE EPSTEIN-BARR VIRAL INFECTION

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Introduction: An atypical chronic active infection caused by herpesviruses and, in particular, by the Epstein-Barr virus (ACA EBV) is a polysymptomatic and polysyndromic, difficult to diagnose and little-studied disease. Often in the ACA EBV the degree of activity of viral infection is not determined. ***Aim:*** To determine biological materials which are the most suitable for detection of the activity of persistent EBV infection. ***Methods***: We studied 98 patients of both sexes aged between 23 and 60 years suffering from the ACA EBV infection. In addition to traditional clinical methods (complaints, anamnesis, physical examination, etc.) and laboratory methods (blood test, etc.), we used PCR method to detect the genome of EBV in biomaterials (blood, saliva, urine, scraping from the tonsils and the posterior pharyngeal wall) using the "Ampli-Sens" test system (Russia). ***Results:*** The detection rate of EBV genome in various types of biomaterials from patients with the ACA EBV infection is different. EBV DNA in saliva is detected in 76.3% of cases, in scraping from the posterior pharyngeal wall – 63.8%, in scraping from the tonsils – 52.7%, but blood and urine have the lowest detection rate of EBV genome – 12.4% and 18.3% consequently. ***Conclusions:*** The highest detection rate of EBV DNA was observed in saliva and scrapings from tonsils and posterior pharyngeal wall. Thus, PCR-diagnostics of EBV genome in these types of biological materials must be used for increasing efficacy of screening of patient with ACA EBV to determine the level of viral activity. Its determination is necessary to make a correct diagnosis of ACA EBV and prescribe a proper medication.

PRIMARY IMMUNODEFICIENCIES

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Immunodeficiencies can be divided into primary (or congenital) immunodeficiency disorders, which are genetically determined, and secondary (or acquired) immunodeficiencies, which may arise as complications of cancers, infections, malnutrition, or side effects of immunosuppression, irradiation, or chemotherapy for cancer and other diseases. Immunodeficiencies are manifested clinically by increased infections, which may be newly acquired or reactivation of latent infections. The primary immunodeficiency syndromes are accidents of nature that provide valuable insights into some of the critical molecules of the human immune system. Most primary immunodeficiency diseases are genetically determined and affect the defense mechanisms of innate immunity (phagocytes, NK cells, or complement) or the humoral and/or cellular arms of adaptive immunity (mediated by B and T lymphocytes, respectively). Although these disorders were once thought to be quite rare, some form of mild genetic immune deficiency is, in fact, present in many individuals. Most primary immunodeficiencies are detected in infancy, between 6 months and 2 years of life, the telltale signs being susceptibility to recurrent infections. Here I present selected examples of immunodeficiencies, beginning with defects in innate immunity and then defects in the maturation and activation of B and T lymphocytes.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

ANALYSIS OF HOMOZYGOUS NONSENSE-MUTATIONS IN ZNF341 GENE AMONG PEOPLE, WHO SUFFER FROM AUTOSOMAL-RECESSIVE FORM OF HYPER-IGE-SYNDROME, AND THEIR ROLE IN CONTROL OF STAT3 GENE EXPRESSION

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Introduction: Hyper-IgE-syndrome (Jobe syndrome) represents as a number of promary immunodeficiency states supported by sharp increasing of IgE in blood serum (more than 2000 ME/ml), characterized by reccurent skin abscesses, predominantly associated with Staphylococcus, eczema and lung infections with forming of bronchiectasis and pneumatocele. There are two forms of hyper-IgE-syndrome, depending on the type of inheritance: autosomal-dominant and autosomal-recessive one. The first form appears due to loss-of-function mutations in gene, which encodes the signal protein and transcription activator STAT3, which provides cell reaction to signals from interleukins and growth factors receptors, and controles the differentiation of Th17, which produce IL17, IL22. The second form of hyper-IgE-syndrome is caused by homozygous nonsense-mutations in gene, which encodes transcription factor ZNF341, which controles STAT3 gene expression by activating its promoter. ***Aim:*** To evaluate how ZNF341 mutations affect STAT3 gene expression, and which role play they in pathogenesis of autosomal-recessive form of hyper-IgE-syndrome. ***Methods:*** Data of medical records of several representatives of four consanguineous families have been analysed. Stop-codones have been identified by sequencing of 6 and 8 exones among affected people and heterozygous carries detected by genealogical analysis. ***Results***: According to data of genealogical analysis there have detected in family A in third generation 3 affected people, in family B –in fourth generation 3 affected people, in family C –in second generation 2 affected people, in family D – in fourth generation 3 affected people, 1 deceased person and 1 miscarriage. Detected homozygous nonsense-mutations of ZNF341 gene inhibit STAT3 gene expression because of its inability to bind to promoter, which lead to decreasing of STAT3 mRNA and as a consequence to violation of T-helpers-17 differentiation and producing of IL17, decreasing of antimicrobial peptide β-defesine-2, which determines the susceptibility of patients with hyper-IgE-syndrome to skin and mucous candidiasis and other opportunistic infections. ***Conclusion:*** Homozygous nonsense-mutations of ZNF341 gene are observed in consanguineous families, they lead to the termination of protein translation and the inability of it to realise its functions.

CLINICAL AND IMMUNOLOGICAL FEATURES OF THE COURSE OF SELECTIVE IMMUNOGLOBULIN A DEFICIENCY

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Introduction: The prevalence of selective immunoglobulin A deficiency (sIgAD) in the world, according to Pereira L.F., et al. (1997) is 1:163 people. In the Russian Federation, the frequency of this primary immunodeficiency, according to RAAKI (2014), is 1: 300 – 1:700 people. Despite the fact that this form of immunodeficiency is the most common form of PID, standard treatment that controls this disease has not been proposed now. ***Purpose:*** Development of clinical and immunological criteria for the course of various forms of selective immunoglobulin A deficiency and assessment of the possibility of a differentiated approach in the treatment of patients. ***Methods:*** In total, 24 patients aged 18 to 42 years were examined (women – 13, men – 11), which are observed in the Center for PID at the Saint-Petersburg Pasteur Institute. The control group consisted of 25 healthy individuals. Evaluation of immune status included the determination in patients of the concentration of immunoglobulins, subclasses of immunoglobulin G in serum and nasopharyngeal washings, determination of subpopulations of lymphocytes and T-helpers. ***Results:*** Various clinical forms of the course of selective IgA deficiency were revealed. In carrying out our study, we found that the concentration of immunoglobulin A in nasopharyngeal washings of patients was reduced only by 1.5 times, and the level of immunoglobulin M was sharply increased in comparison with those of practically healthy individuals. There was also an increase in the level of Tfh2, Tfh1 cells in patients with sIgAD. However, the revealed feature requires further study and statistical processing. ***Conclusions:*** The analysis of the clinical course of selective immunoglobulin A deficiency and the parameters of humoral immunity suggests a connection between the features of the course of the disease and the humoral profile of patients.

CHARACTERISTICS OF CELLULAR AND HUMORAL IMMUNITY IN CHILDREN WITH CYSTIC FIBROSIS

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Cystic fibrosis is one of the most common hereditary diseases that have an autosomal recessive type of inheritance. The aim of the study was to study the peculiarities of the state of cellular and humoral immunity in children with cystic fibrosis. On the basis of the medical center of pediatrics, 36 children with cystic fibrosis, aged 4 to 8 years, were examined. Among them 26 (72.2%) – children with a pulmonary form, 4 (11.1%) – with a mixed form and 6 (16.7%) – with an intestinal form. The examination was carried out both in the exacerbation phase in 21 (58.3%) patients and in the remission phase in 15 (48.3%) patients. The control group consisted of 17 children of the corresponding age. The quantitative content of subpopulation composition of lymphocytes in peripheral blood was studied by immunofluorescence method. The concentration of IgG, IgA and IgM was determined in serum by ELISA. The main complaints of patients were a decrease in appetite

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(86.2%), headaches (58.2%), sleep disturbances (30%), fast fatigue (71.6%), mood changes (86.3%), constipation (84%). The examination revealed the following: pallor of the skin (100%), physical retardation (36.3%), allergic reactions (26.7%), decreased physical activity (48.4%). The analysis of the results showed that the immunological parameters of cystic fibrosis differ from those of the control group. Comparative characteristics of the relative content of T-lymphocytes and its subpopulations ($CD4^+$- and $CD8^+$-cells) in children with MV revealed their significant decrease ($p<0.05$), but the deepest deficit is observed in exacerbation ($p<0.01$). Significantly low expression of CD16 antigens on lymphocytes in sick children ($p<0.05$) and a reduced level of phagocytic activity may indicate a weak resistance of the body. Comparative characteristics of circulating $CD20^+$- cells showed that their level was significantly increased with the maximum value during exacerbation ($p<0.01$) in MV. IgG and IgA levels were reduced and IgM was significantly elevated in exacerbation ($p<0.01$). Thus, various clinical conditions of cystic fibrosis correspond to certain immune disorders that determine the severity and degree of progression of the process.

ETIOLOGICAL STRUCTURE OF SECONDARY IMMUNODEFICIENCY

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Introduction: Secondary immunodeficiency-diseases that do not have genetic causes and are the most common form of pathologic people. The most interesting are antenatal immunodeficiency, as the basis of a huge variety of pathological conditions in the subsequent stages of postnatal ontogenesis. Aim: Study of the etiological structure of secondary immunodeficiency ***Methods:*** The study involved 171 children from mothers with different types of gestation. The comparison groups were presented as follows: I gr. – 60 children, from women with a physiological course of pregnancy; II gr.– 57 children, women with the threat of termination of pregnancy; III gr. – 54 children, from a woman with OPG-gestosis. Design of the study included ultrasound of the fetoplacental complex, etiological studies of the mother's blood (TORCH-complex), placenta, resistance assessment in children of the first year of life, etiological studies in children (TORCH-complex). ***Results:*** In children born to women with physiological pregnancy, in the first year of life parameters of CPR and physical age corresponded, the resistance index was high. The rate of secondary immunodeficiency was 11.66% (n=7). In the history of 4 women in the blood of ELISA were determined specific antibody titers to 4 type of herpes, 3, at the time of 32 and 34 weeks. was diagnosed in utero hypoxia. In group II children, the frequency of szrp and IUGR amounted to 40.35% 31.57%, respectively, the resistance index of the edge due to allergies. Immunodeficiency was diagnosed in 36.84% of cases (n=21), the cause was severe intrauterine hypoxia and asphyxia. In group III, the incidence of psrp and IUGR was 24.07% and 20.37%, respectively, the resistance index is low, due to frequent infectious diseases. Secondary immunodeficiency was recorded in 43 children (79.62%). The cause was intrauterine infections, with the share of infections of the herpes family accounted for 88.37%. The incidence of 4 types of herpes was 84.21% in this group. ***Conclusions:*** Thus, the etiological structure of secondary immunodeficiencies was represented as follows: in the first place of the herpes family infection, in particular, 4 types of herpes; the second place is chronic oxygen starvation. The presented two leading factors of alteration are the basis for the formation of antenatal immunodeficiency in children.

THE DEFEAT OF THE CARDIOVASCULAR SYSTEM WITH HAART OF HIV

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The analysis of the current state of the problem allows us to recognize that the number of people living with HIV/AIDS (PLWHA) has increased in recent years and, accordingly, the incidence of morbidity and mortality from CVD has increased.In the pathogenesis of SSP, incl. HAART plays the main role in the progression of atherosclerosis. Atherosclerotic changes and dyslipidemia associated with PI intake are due to the presence of homology between the catalytic region of the HIV-1 protease, which is the point of application of PI, and two human proteins involved in the regulation of lipid metabolism: cytoplasmic protein-1 binding retinoic acid (CRABP-1), and a low-density lipoprotein-protein receptor (LRP), insulin resistance is due to inhibition of the function of the B-cell PI. There is an increase in the frequency of apoptosis of adipocytes and a decrease in the differentiation of preadipocytes into adipocytes, resulting in a decrease in triglyceride stocks and an increase in lipid consumption. Violation of the capture of hepatic chylomicrons and endothelial clearance of triglycerides ultimately leads to hyperlipidemia and insulin resistance. The infection of HIV cardiomyocytes with changes in membrane autoantigens, activation of MF and secretion of pro-inflammatory cytokines with autotolerance disorder stimulates the synthesis of anti-a myosin AT, alteration and apoptosis of cardiomyocytes with the development of fibrosis. HIV retains high rates of CRP, IL-1,6, TNFα, which supports inflammation, damages the endothelium and changes the metabolism of plasma LPs, decreasing HDL and increasing LDL, triglycerides, which supports the development of atherosclerosis. Recurrences of ACS are combined with high viral load and hyperlipidemia, pulmonary hypertension is accompanied by a high level of GP120, with myocarditis in the blood elevated titre of anti-a myositis antibodies. In PLWHA, CVD is formed at a young age and is characterized by acceleration of progression of pathology. When receiving HAART, the lipodystrophy that is formed the cause of formation of CVD on the background of therapy, but the mortality from cardiomyopathies decreases. Early diagnosis and therapy reduce mortality.

International Journal on Immunorehabilitation
2019 Volume 21 No 1

REFLEXOTHERAPY EFFECT ON THE IMMUNE STATUS IN THE EARLY RECOVERY PERIOD OF ISCHEMIC STROKE

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In Russia, stroke affects more than 500 000 people annually, ranking second in the frequency of deaths among circulatory system diseases. The ischemic process is accompanied by both immune (hyperproduction of IL 1 and 2, TNF-α, etc.) and hormonal (through affecting the anterior lobe of the pituitary gland) by changes, which increases the risk of infectious and inflammatory complications that worsen the outcome of a stroke. The usage of drug correction of immunological disorders, in addition to the high cost of drugs, is accompanied by a risk of side effects, whereas the use of reflexotherapy (RT) methods, tested for centuries, with immunoregulatory effects, practically does not cause complications. The aim of this research was to study immune status (IS) among patients in the early recovery period (ERP) of ischemic stroke (IS), depending on the treatment performed in the acute period (AP). The immunological study was conducted in the primary vascular center of Blagoveshchensk dynamically between two groups of patients representative of the severity of stroke, age and gender, aged 54 to 78 years (mean age 65.7 2.1 years) for 2 days and 2 months after suffering IS. The patients of the main group (15 persons), except for the baseline treatment, received RT procedures with acupuncture points with immunoregulatory action, the second group (control group, 15 people) – only standard treatment. In the main group, after two months, there remained significant improvement in IC performance: reducing the total content of leukocytes ($p<0.05$), increasing the level of lymphocytes ($p<0.05$), T-lymphocytes (CD3+) ($r<0.01$) and T-helpers (CD4+) ($p<0.05$), a decrease in the number of β-lymphocytes to normal values ($p<0.01$), and an increase in the IgG level ($p<0.05$). In the control group, immunological disorders persisted, and two cases of post-stroke pneumonia and one exacerbation of chronic pyelonephritis were documented. Thus, the inclusion of RT in the complex of early rehabilitation in the AP of IS allows minimize immunological disturbances in the ERP and improve the prognosis of the disease, reducing the susceptibility of patients to the development of infectious complications, which allows us to recommend the use of RT in the AP of IS for their prevention.

NON-PHARMACOLOGICAL CORRECTION OF ENDOTHELIAL DYSFUNCTION AND ARTERIAL STIFFNESS IN THE ACUTE PERIOD OF STROKE

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In Russia, stroke affects more than 500 000 people annually, ranking second in the frequency of deaths among circulatory system diseases. The ischemic process is accompanied by both immune (hyperproduction of IL 1 and 2, TNF-α, etc.) and hormonal (through affecting the anterior lobe of the pituitary gland) by changes, which increases the risk of infectious and inflammatory complications that worsen the outcome of a stroke. The usage of drug correction of immunological disorders, in addition to the high cost of drugs, is accompanied by a risk of side effects, whereas the use of reflexotherapy (RT) methods, tested for centuries, with immunoregulatory effects, practically does not cause complications. The aim of this research was to study immune status (IS) among patients in the early recovery period (ERP) of ischemic stroke (IS), depending on the treatment performed in the acute period (AP). The immunological study was conducted in the primary vascular center of Blagoveshchensk dynamically between two groups of patients representative of the severity of stroke, age and gender, aged 54 to 78 years (mean age 65.7 2.1 years) for 2 days and 2 months after suffering IS. The patients of the main group (15 persons), except for the baseline treatment, received RT procedures with acupuncture points with immunoregulatory action, the second group (control group, 15 people) – only standard treatment. In the main group, after two months, there remained significant improvement in IC performance: reducing the total content of leukocytes ($p<0,05$), increasing the level of lymphocytes ($p<0.05$), T-lymphocytes ($CD3^+$) ($r<0.01$) and T-helpers ($CD4^+$) ($p<0.05$), a decrease in the number of β-lymphocytes to normal values ($p<0.01$), and an increase in the IgG level ($p<0.05$). In the control group, immunological disorders persisted, and two cases of post-stroke pneumonia and one exacerbation of chronic pyelonephritis were documented. Thus, the inclusion of RT in the complex of early rehabilitation in the AP of IS allows minimize immunological disturbances in the ERP and improve the prognosis of the disease, reducing the susceptibility of patients to the development of infectious complications, which allows us to recommend the use of RT in the AP of IS for their prevention.

PERSONALIZED APPROACH TO THE SELECTION OF IMMUNOTROPIC DRUGS

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Immunity of a person is plastic; it can be affected by changes in the external and internal environment. Differences in the immune status (IP) are established depending on different factors. In other cases, IP changes due to the presence of pathology, which leads to a change in the activity of the immune system, which can be hidden and obvious. All this requires the selection of adequate therapy. However, not all people will have a similar reaction to a particular drug. Little attention is paid to in vitro drug testing, when it is possible to evaluate the effect of a particular preparation on the proliferative activity and the synthetic ability of cells. The proposed approach includes a preliminary study in vitro of the functional activity of

ISSN 1562-3629

immune cells after their incubation with drugs. As an example, we give an investigation of the effect of cycloferon on the phagocytic activity of peripheral blood leukocytes (PBL). Peripheral blood of 9 healthy donors was received in the morning on an empty stomach. In the 1st portion, cycloferon was added at a final concentration of 0.005 mg/ml, which corresponds to the maximum of the drug in the blood after oral administration (Sukhanov et al., 2012). The corresponding volume of saline was added to the 2nd portion. The samples were incubated for 60 minutes at 37°C, after which the phagocytic activity of the PBL was evaluated according to (Shilov et al., 2003). The stimulation index was calculated as the ratio of the index in the non-stimulated sample to the same index in the sample stimulated by cycloferon. An index greater than 1 indicated a stimulating activity of the drug. If the index was less than or equal to 1 - the drug had no effect at all or reduced the activity of the cells. So, among 9 healthy volunteers, cycloferon stimulated phagocytic activity in only 55.5%. In 22% of donors, the drug did not change the activity of the PBL, while in the remaining ones it decreased somewhat. Such individual character of the response of the human immune system presupposes the necessity and validity of using a personalized approach to the selection of immunotropic therapy, which can be successfully served by studying the activity of drugs in vitro using individual images of blood or cells of the immune system.

APTAMERS ARE ANALOGUES OF MONOCLONAL ANTIBODIES

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Introduction: Immunochemical analysis based on an antigen-antibody reaction, is the most widely used in medicine. The use of monoclonal antibodies to increase the specificity and sensitivity of the test systems, which are widely used in biology and medicine over 30 years as diagnostic molecules and therapeutic targeted drugs. In recent years, monoclonal antibodies have been developed for the treatment of oncological diseases especially intensively. The technology for production of monoclonal antibodies was described by G. Köhler and S. Milstein in 1975 and up to the present time did not any major change. A number of important technological and biological advantages over antibodies have aptamers - synthetic molecules of nucleic acids made to specific targets. Simplicity of synthesis and modifications allows producing and applying aptamers for research, diagnostic and therapeutic purposes. They have uniform activity irrespective of the synthesis series, much smaller than antibodies, so it is easier to penetrate into tissues and cells may have higher affinity and specificity.

Aim: With the example of DNA of aptamers of thrombin inhibitors, to show or exclude intermolecular interactions with other targets - serum proteins. Subjects of study: aptamers thrombin inhibitors 31RE and 31RE complex with protamine.

Methods: Immunoelectrophoresis in agarose and electrophoresis in PAAG followed by identification of proteins and aptamers with specific dyes and antibodies to proteins with known molecular weight. Molecular markers of a wide range were also used.

The results of a series of laboratory experiments showed the absence of complexes of aptamer 31RE with any identifiable proteins of serum. Its electrophoretic mobility was identical in experiment and control in all series, which may indicate the reliability of the results obtained. However, a partial and possibly reversible interaction of the aptamer-protamine DNA complex with albumin was recorded during the period of presence in the blood. This fact can be explained by the presence of protamine.

Conclusion:The data obtained will accelerate the promotion of the DNA aptamer of thrombin inhibitors in medical practice as a new generation of anticoagulants.

DYNAMIC TRANSFORMATION OF THE PHENOTYPE CD16+CD32+CD11B+ NEUTROPHILIC GRANULOCYTES IN HEALTHY HUMAN PREGNANCIES

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The immune system ensures the maintenance of immune tolerance in pregnancy, necessary for the development of semi-antigenic fetus, while preserving anti-infection protection potential. Neutrophilic granulocytes (NG) play the key role in the adaptation to pregnancy: neutrophilia, activation of phagocytosis, formation of NET, the appearance of subsets of NG, inducing Treg, showing angiogenic properties. In this case, the features of phenotype transformation of various subsets of NG during pregnancy are not fully studied. The aim of this study is to study the phenotypic features of $CD16^+CD32^+CD11b^+$NG during the I-III trimesters of a physiological pregnancy.

Methods: 30 blood samples of pregnant women of I, II, III trimesters (groups 1, 2, 3, n=10 in each group) and 10 non-pregnant women (control), 25–27 years old, were examined. Flow cytometry was used to determine: % NG, carrying CD16, CD32, CD11b and their expression density (MFI).

Results: It was established that NG subset with $CD16^+CD32^+CD11b^+$ phenotype in all studied groups was 97.2% [94.27;98.32], but significantly differed in MFI. In group 1 MFI CD32 decreased 3.5 times (3.69.[3.58;3.76] *vs* 12.3[8.76;15.08] in the control, $p<0,05$), MFI CD16 in 1.6 times (20.62[16.34;23.83] against 32.1[23.35;34.75] in the control, $p>0.05$), while the MFI CD11b increased by 1.5 times (27,35[26.8;27.76] against 18.0[12.6;25.45] in the control, $p<0.05$). In II trimester, the transformation of $CD16^+CD32^+CD11b^+$NG was revealed: against a background of a decrease in MFI CD16 by 1.5 times in comparison with group 1 and 2-fold with respect to control and MFI CD11b to the control level, there was an increase in MFI CD32 in 2.4 times with respect to group 1, not reaching the control values. III trimester is characterized by significant activation of NG in comparison with the control and with groups 1 and 2, manifested in increase in

International Journal on Immunorehabilitation
2019 Volume 21 No 1

the expression level of all studied receptors: MFI CD16 to 36[34.65;37,43]; MFI CD32 to 16.96[16.89;17.33]; MFI CD11b to 34.1[30.65;37.4].

Conclusion: Dynamic transformation of the phenotype of the $CD16^{+}CD32^{+}CD11b^{+}$NG subset observed in various trimesters of healthy pregnancy is necessary to maintain a delicate balance between proinflammatory and anti-inflammatory properties of NG, which ensures a normal course of pregnancy.

THE CONTENT OF T, B, AND NK LYMPHOCYTES IN INFANTS BORN AS A RESULT OF IN VITRO FERTILIZATION (IVF)

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In single studies it was shown that in infants after IVF there are violations adaptive and innate immunity. At the same time, there are very few studies on the immunity of young children after IVF. The aim of the study was to analyze the results of immunophenotyping of peripheral blood lymphocytes of infants born as a result of IVF. ***Methods:*** We analyzed the relative and absolute values of CD3, CD4, CD8, CD19, CD16, 56 cells of peripheral blood of 9 children aged 2–16 months (8.0 1.43 months) born as a result of IVF. The results were compared with reference values. Immunophenotyping was carried out on flow cytofluorimeter FC500. Statistical processing of the material was carried out using Microsoft Excell. ***Results:*** The study found that 88.9% of children conceived with IVF were born prematurely; while 44.5% of children from single-child pregnancy, and 55.5% from multiply pregnancies. In peripheral blood, the total number of CD3-lymphocytes was normal in all the examined subjects, and in 55.5% of children an imbalance in T-lymphocyte subpopulations due to a decrease in CD8-lymphocytes was detected. It should be noted that 80% of children with low CD8-lymphocyte counts are born from multiple pregnancies. Reduction of CD4-cell content was noted only in 11.1% of children. The indices of IRI (CD4 / CD8) reflected the imbalance of T-lymphocyte subpopulations and were increased in 22.2%, and in 11.1% they were lowered. The level of B-lymphocytes in 66.7% remained within the age limit. There was no absolute deficit of B cells, moreover, in 33.3% of children the CD 19 B-lymphocyte content was higher than normal. The number of NK cells that play an important role in the first line of protection against viral and tumor diseases in 44.4% of children was below normal. ***Conclusions:*** 1. The results of the pilot study show that children of the first year of life conceived with the help of IVF are more likely to be born prematurely, and the immunogram indicators do not correspond to the norms of children conceived naturally 2. There is a deficit of CD8 T-lymphocytes and NK-cells; the CD19 B-lymphocyte content corresponds to the age norm or exceeds it.

THE SPECTRUM OF AUTOANTIBODIES IN WOMEN WITH RECURRENT PREGNANCY LOSS

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Introduction: In the obstetric and gynecological practice, the synthesis of autoimmune antibodies is associated with a number of pathological conditions during pregnancy: miscarriage, antenatal fetal death, venous thrombosis, thrombocytopenia, gestosis (including severe and prognostic adverse), the development of chronic placental insufficiency.

Objective: To analyze the content of autoantibodies detected in peripheral blood in women with recurrent pregnancy loss.

Methods: Clinical and laboratory examination of 70 pregnant women with an episode of one or more miscarriages in history was conducted. The level of autoantibodies to beta-2-glycoprotein-1, cardiolipin, annexin 5, human chorionic gonadotropin (HCG) and prothrombin was determined in the peripheral blood serum of women by enzyme immunoassay using commercial test systems Orgentec Diagnostika GmbH (Germany), Diatech-EM LLC (Russia).

Results: When analyzing the findings, it was found that the most frequently in analyses of women with miscarriage in pregnancy, autoantibodies to the chorionic gonadotropin were detected in 42.9% of cases. Autoantibodies to cardiolipin were found in 14.3% of women, antibodies to beta2-glycoprotein-I were detected in 22.9% of cases, antibodies to annexin 5 were found in 20.0% of women, antibodies to prothrombin were found in 11.4% of cases. A combined increase in antibodies to β2-glycoprotein-I and cardiolipin was observed in 11.4% of cases. For the note that antibodies to chorionic gonadotropin and annexin 5 occurs mainly in isolation.

Conclusion: In that way, on the basis of the obtained results, it can be concluded that the presence of autoimmune antibodies, such as antibodies to beta-2 glycoprotein-1, cardiolipin, annexin 5, has a great pathogenetic significance in the clinic of miscarriage. According to our data, the increased content of antibodies to HCG could occur in early pregnancy termination. The adverse effect of antibodies to human chorionic gonadotropin on reproductive processes, especially during pregnancy, seems to be associated with the direct suppression of the biological activity of human chorionic gonadotropin.

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IMPACT OF RADIOFREQUENCY ABLATION ON PLASMA CYTOKINES IN PATIENTS WITH UNRESECTABLE LIVER CANCER

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Introduction: Radiofrequency ablation is widely accepted interventional approach for liver cancer and has the advantages of high treatment efficacy and low complication risk. The various studies, including ours, have reported the immunomodulatory effects of RFA procedure on primary and metastatic liver cancer. The aim of this study was to explore the influence of RFA on the factors of tumor microenvironment including plasma cytokines. ***Methods:*** 10 patients aged 39 to 72 years (mean 55.1±11.2 years) with unresectable primary and metastatic hepatic tumors underwent RFA. Blood samples were collected from each patient and plasma cytokines (TGF-β, IL-10, IL-17, INFγ), were measured before and after 1 and 3 month of RFA treatment. Healthy age-matched volunteers were used for group comparison. Mann–Whitney U test, Mc Nemar test and Wilcoxon rank test were applied for intergroup comparisons as appropriate. ***Results:*** Serum IL-17, IL-10 and TGF-β levels were elevated in the patients with liver cancer compared to healthy volunteers. Decreased IL-10 and INFγ levels were reported after 1 and 3 month of RFA procedure, whilst there were no significant changes in TGF-β and IL-17 levels after RFA treatment. ***Conclusion:*** Changes in plasma cytokine levels in patients treated with RFA further edits the evidence on the immunomodulatory effects of RFA on tumor microenvironment.

SPECIFITY OF THE IMMUNE RESPONSE AFTER VIRUS-BASED DRUGS ADMINISTRATION IN PATIENTS WITH PANCREATIC CANCER

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Pancreatic cancer is one of the most aggressive types of cancer: medium survival is about 11–19 months, five-year survival on advanced stages is no longer than 8%. Disease has prolonged asymptomatic period, and patient is often visits the doctor having an advanced cancer. Standard therapy is low-effective, and specialists thoroughly consider innovative virus-based drugs which have selective effect on tumor cells. For example, reovirus (Reolysin) invaded only cells with mutation in K-ras, typical for pancreatic cancer. After therapy with reolysin, carboplatin and paclitaxel patients demonstrated increased levels of IL-10, VEGF-A, RANTES, which proves proinflammatory effect of the drug, and the level of CD4+ and CD8+ with activation markers CD71, CD95 and maturity marker CD45RO. These lymphocytes had increased number of CTLA4, which gives a reason to consider investigation of reolysin, chemotherapy and checkpoint inhibitors combination. Recombinant viruses can be used as vectors for anti-tumor genes. Adenovirus LOAd703 was inserted the gene of ligand protein 4-1BBL. This receptor is located on active T-lymphocytes, NK-cells, monocytes, neutrophils and macrophages. Its interaction with the ligand stimulates proliferation and differentiation of innate immunity cells, especially NK-cells. After the incubation of tumor tissue, lymphocytes and monoclonal antibodies specific for 4-1BB, the number of lymphocytes infiltrated the tumor was significantly increased. T-VEC, modified herpes simplex virus 1 carries gene of granulocyte-macrophage colony-stimulating factor (GM-CSF). Its effect is based on the tumor cells destruction and on anti-tumor immunity stimulation: dendrite cells activation, decrease in number of regulatory and suppressive T-lymphocytes and increase in number of cytotoxic ones. Oncological Cluster of Sechenov University plans to carry out the investigation comparing the effectiveness of virus-based drugs already used in therapy of melanoma and head and neck cancer, as well as defining the most effective combination of virotherapy and standard cancer treatment.

ERBB2-SPECIFIC ADDRESS TOXIN DARPIN-LOPE: EXPLORING TOTAL TOXICITY AND IMMUNOGENICITY *IN VIVO*

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Today medicines which are based on monoclonal antibodies are applied for the treatment of many different diseases, occupying the most part of biopharmaceutical market. Nevertheless, the lack of efficiency of such chemicals makes the problem of exploring alternative therapeutic agents relevant. One of potential solution is address toxins which consist of guide and effector modules. The molecules of DARPins are alternative frame proteins of non-immunoglobulin nature which contain ankyrin repeats. ERbB2-specific address toxin DARPin-PE40 has been constructed in the laboratory of molecular immunology IBCh RAS. Its selective cytotoxic effect was proved *in vitro* and potent antitumor activity was demonstrated *in vivo* on xenograft model of breast cancer in immunodeficient mice. This work is devoted to the study of toxic and immunogenic properties of anticancer ErbB2-specific address toxin DARPin-LoPE in immunocompetent mice. As recombinant proteins which contain fragments of bacterial toxins provoke immune reactions, cytotoxic module of DARPin-LoPE was adapted for using in therapy – it is low immunogenic fragment of pseudomonas aeruginosa toxin without B-cell epitopes. ErbB2 – is a specific target of examined protein belongs to the epidermal growth factor receptor family. The overexpression of ErbB2 occurs in 20–30% of breast cancer. The ErbB2-specific recombinant proteins DARPin-PE40 and DARPin-LoPE were expressed in E. coli and then purified using Ni2+-NTA affinity chromatography and ion-exchange chromatography. Selective cytotoxic activity of proteins was proved on ErbB2-overexpressing cell line SKBR-3 using MTT test – IC_{50} for

International Journal on Immunorehabilitation
2019 Volume 21 No 1

DARPin-PE40 was 0.1 pM, IC_{50} for DARPin-LoPE was 16 pM. Examined proteins were injected into BALB/c mice. A potential toxic effect of DARPin-PE40 and DARPin-LoPE was evaluated by controlling weight changes of animals, measuring of hepatic aminotransferases activity and blood leukocyte count. Total immunogenic properties were observed using an analysis of specific antibody titer in the blood serum with enzyme-linked immunosorbent assay. We have found out that DARPin-LoPE demonstrates significantly lower total toxicity *in vivo* than DARPin-PE40, moreover, either proteins have comparable efficiencies in vitro, that makes DARPin-LoPE perspective agent for designing anticancer drugs.

PROSTAGLANDIN E2 PRODUCTION WITH TUMORS AND INFLAMMATORY DISEASES OF THE PROSTATE

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Introduction: Factors that have a suppressive effect on the tumor process attract attention of many researchers. These factors include prostaglandins (PG), which, as other immunosuppressive factors, have a wide range of effects. A comparative assessment of the effect of various PGs on tumor growth has shown that prostaglandin E2 (PG E2) plays a key role in the suppressive effect. He is produced by many tumors and is therefore often regarded as a marker for the progression of tumor growth (N.M. Berezhnaya, V.F. Chehun). A study of the role of PGE2 in prostate diseases was initiated at the Astrakhan Medical University more than 10 years ago (D.M. Nikulina, V.M. Miroshnikov, P.A. Ivanov, K.S. Seidov). The aim is to make a comparative analysis of the results of laboratory determination of PGE2 in blood serum and prostate secretion samples of patients with benign prostatic hyperplasia (BPH), prostate cancer (PCa), chronic prostatitis (CP) and male infertility (MI), and in blood samples of healthy men. ***Results:*** It was found that PGE2 concentration in the blood in all prostate diseases is different from the values in the group of healthy men. Most interesting was the fact of decrease compared to donors PGE2 concentration in the blood of patients with BPH and PCa in average 2-3 times (respectively 1100–1300 and 400–500 pg/ml). PGE2 levels in blood serum of patients with prostate tumors is reduced more than in inflammation. And its concentration in prostate secretion increases with PCa and BPH dozens of times. After complex treatment, PGE2 decreased in the prostate secretion. Results similar with HP data, obtained for male infertility. ***Conclusions:*** Regularity of PGE2 synthesis in the altered prostate and its secretion into biological fluids can be used for differential diagnosis between PCa and CP. The fact that PGE2 concentration in the prostate secret is more than in the blood is possible to use the PGE2 test for noninvasive diagnosis of diseases of the prostate.

STUDY OF TLR LIGAND AND CXCL12 INFLUENCE ON THE CANCER CELL MIGRATION

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Indroduction: In the recent decades the numerous studies have been conducted on the research of chemokine and Toll-like receptor (TLR) influence on tumor formation. Not all components of these factors are completely understood. Thus the aim of our study is to study a migration of mononuclear and cancer cells toward CXCL12 and TLR ligand. ***Methods:*** There were used culture line K562, mononuclear cells (MNC) in healthy donors and donors with myelomonocytic leucosis before and after chemotherapy. Factors for chemotaxis were CXCL12 (ThermoFisher, USA) and synthetic ligands (DNA_lig and RNA_lig). The chemotaxis was studied by using Boyden's chamber 96-Well Filtration Plate Multiscreen – MIC with 5 mkm pores. The statistical analysis has done by using BioStat 2009 5.8.30**.** ***Results:*** the CXCL12 induced MNC chemotaxis in healthy donors was significantly higher than intact cell chemotaxis 2 times. The MNC migration in healthy donors and donors with myelomonocytic leucosis toward DNA_lig and RNA_lig was significantly lower than control by half. The K562 and myelomonocytic leucosis cell migration toward CXCL12 was significantly lower than the induced migration of cells in healthy donors 6 times. The MNC migration from donors with myelomonocytic leucosis after chemotherapy was significantly higher than MNC migration from donors before chemotherapy 2 times. Conclusion: the results indicate that the chemotaxis was in both healthy and cancer cells toward DNA_lig and RNA_lig is significantly lower than in the control which may suggest a suppressive influence of these ligands on cell migration. This may be used in a preventing of cancer cell metastasis. Cancer cell migration is strongly lower than chemotaxis of MNC in healthy donors and increases with the use of chemotherapy which could be the cause of homing disorder in bone marrow. In the future we are planning to research the TLR and chemokine receptors gene expression in cancer cells by above factors in order to understanding possible relation between these innate immunity factors (chemokine network and TLRs).

MORPHOFUNCTIONAL STATUS OF NEUTROPHILS IN LARYNX CANCER PATIENTS

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Actuality: Laryngeal cancer is mainly found in men aged 40 to 60 years, constituting 80–95% of patients, and occupies the 5th place in the structure of morbidity in the male population. The attention of researchers around the world is drawn to

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the relationship between the developing tumor and the immune system. The results of recent studies have demonstrated that neutrophilic granulocytes (NG) are actively involved in the implementation of pro- and antitumor reactions.

Purpose: To evaluate the structural and functional properties of neutrophils in larynx cancer patients.

Methods: 35 people were examined: 15 persons of a main group (larynx cancer patients) and 20 healthy persons. The object of the study was venous blood, in which it was estimated: the total number of leukocytes, the leukocyte formula, the degree of segmentation of the NG nuclei, neutrophil-lymphocytic ratio (NLR), NBT-test. In the serum by ELISA determined cytokines that regulate the functional activity of NG: IL-8 and IL-18.

Results: In the blood of cancer patients an increase in the relative content of NG (p=0.022) and a decrease in the absolute number of lymphocytes (p=0.015) were revealed in relation to the comparison group. As in many articles by other authors, we noted an increase in NLR (p=0.024) in patients. Structural features of neutrophils were manifested in an increase in the number of hypersegmented NG (p= 0.001), as well as in an increase in the average segmentation coefficient (p=0.024). The number of NBT-positive NG in the main group was 1.7 times higher than in the comparison group (p= 0.01). The concentration of cytokines stimulating the activity of neutrophils in the serum of cancer patients also exceeded the values of the comparison group: IL-8 – 2.3 times more (p=0.007); IL-18 – 1.6 times more (p=0.007).

Conclusion: Circulating neutrophils in patients with laryngeal cancer have a number of structural and functional features, indicating the activation of the phagocytic link of the immune system on the background of malignant growth.

INDICATORS OF CELLULAR IMMUNITY IN PATIENTS WITH TRAUMATIC BRAIN INJURY AND THE PROSPECTS FOR CLINICAL AND IMMUNOLOGICAL PROGNOSIS OF THE COURSE OF THE DISEASE OF VARIOUS SEVERITY

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Introduction: According to the World Health Organization, traumatic brain injury (TBI) is currently the third most common cause of overall mortality. However, the status and role of the immune system in the formation of clinical manifestations, possible complications in victims with TBI is still a poorly studied problem.

Aim: Development of clinical and immunological algorithms for prediction of complications of traumatic brain injury of various severity in the acute period of the disease.

Methods: Two groups of patients were identified: patients with an TBI of varying severity (n=13) and a control group, relatively healthy individuals (n=40). The main methods of examining patients included assessing the somatic and neurological status of patients, as well as assessing the immune status of patients.

Results: When examining patients, 10 cases of brain concussion, 3 cases of brain contusion of mild and medium severity were revealed. When carrying out an immunological examination of patients we found a significant increase ($p<0.05$) in the number of $CD3^+CD4^+$ (Th17/Th22), naive Th (Th17/Th22, Th1/Th17, DP Th17, Tfh17/Tfh22, Tfh1/Tfh17). There was also an increase in the number of memory cells. Among them significantly ($p<0.05$) CM Th (Th17/Th22, Th1/Th17, Tfh17/Tfh22) and EM Th (Th17/Th22) cells increased. Significant reduction of cells ($p<0.05$) have been identified among the following subpopulations: $CD3^+CD4^+$ (Th1, Th2), CM Th (Th1, DP Th17) and EM Th (Th1).

Conclusions: As a result of the studies, a significant change in the indices of cellular immunity was revealed in patients with TBI of varying severity, which suggests a correlation between the severity of the trauma and the immune status.

ANTIGEN AND MOLECULAR-GENETIC MARKERS OF DIAGNOSTICS AND PROGNOSTICATION OF UROTHELIAL CANCER

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Introduction: Urothelial cancer (UC) occupies a 3th place among urooncological diseases. The most highly immunogenic antigens are cancer-testicular antigens (CTA). Their expression and intercommunication with genetic mutations at UC small studied. Aim of work – to conduct the comparative analysis of expression of CTA and molecular-genetic mutations at different clinical forms UC.

Methods: Studied 24 standards tumors from that 18 (75%) were presented by a muscularly-invasion form (MIF) and 6 (25%) muscular-non-invasive form (MNIF) of UC. Expression of CTA was estimated by the method of running cytometry on the vehicle of FACS Canto II with using of antibodies to CTA: MAGE (FL – 309), GAGE3 (N10), BAGE (R - 15), NY – ESO – 1 (E978) (Santa Cruz Biotechnology, USA). The mathematical processing of data was conducted on the basis of package of statistical softwares of SPSS 23.0 for Windows. Statistically the values of c considered meaningful by a confidence interval no less than 95%, at $p\leq0.05$.

Results: It is set that for patients with MIF UC expression of NY – ESO – 1 was in 7 (38,9%); MAGE in 15 (83.3%); GAGE in 8 (44.4%) and BAGE – in 9 (50%) cases. 2 types of tumor expressed all 4 studied CTA (11,1%), 5 - three from 4th CTA (27,8%). Expression a minimum of one CTA was revealed in 88.9% cases (16 standards). In the standards of MNIF UC expression of NY – ESO – 1, MAGE and BAGE registered in separate standards (on one antigen in every tumor), that made on 16.7% cases for every CTA. GAGE was educed in 2th standards (33.3%). In 2th standards expression of CTA was absent, and in 2 determined expression at once 2th studied CTA (33.3%). In 66,7% cases was presented one of 4th stu-

International Journal on Immunorehabilitation
2019 Volume 21 No 1

died CTA. Research of molecular-genetic mutations showed that all investigated tumor cultures had had characteristic for UC of change: deletion of 9 chromosomes (66,7%), absence of Y– of chromosome (50%) and monosomy of 13 and 17 chromosomes (33.3%). In solitary instances registered changes in chromosomes 1, 3, 7 and trisomy of 7 chromosomes. The increase of genetic mutations was also shown at growth of degree of invasion and with an increase in malignancy of UC. Comparative study of molecular-genetic and antigen changes in the process of progress of tumor at educed UC reliable correlation ($p \leq 0.05$) of growth of expression of CTA (GAGE, BAGE, MAGE and NY – ESO – 1) with the level of genetic mutations.

Conclusion: Thus, study expression of CTA (MAGE, BAGE, NY – ESO – 1, GAGE) and level of genetic mutations can be perspective for early diagnostics, prognostication of progression and end of illness.

PSYCHOLOGICAL FEATURES OF CHILDREN WITH BRONCHIAL ASTHMA

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Goal: Identify the psychological characteristics of children with bronchial asthma.

Methods: The study included 40 children with bronchial asthma from the age of 7 to 17 years. A specially developed questionnaire was filled out for all children, including: history of life and disease, laboratory and instrumental studies, and the Child Depression Rating (CDI) M. Kovach, information about the hobbies available, Shevchenko MA test "Beautiful drawing". The data was statistically analyzed using the Microsoft Office Excel 2007 program.

Results: Depending on the severity of the disease, the children were divided into three groups: 1– lung BA (n=15), 2 – moderate BA (n=7) and 3 – with severe asthma (n=7). The newly diagnosed asthma was isolated (n=11). According to the test of M. Kovac and the "Beautiful figure", a decrease in mood was significantly more frequent among children with asthma of moderate severity compared with a severe and newly diagnosed asthma (90% *vs* 71% and 73%, with $p<0.02$) and did not occur in mild asthma. Interpersonal problems are typical for children with asthma of moderate to severe severity compared with children with mild and newly diagnosed asthma (90% and 85% vs. 40% and 45%, with $p<0.001$). Anodonia, the presence of a sense of loneliness, also significantly more prevalent in children with asthma of moderate to severe severity compared with children with mild asthma (71% vs. 33%, $p<0.001$), but were also characteristic for children with newly diagnosed asthma (63%). The depression level was above average in almost all children with asthma of moderate and severe severity (90% and 100%) and one in three children with asthma of mild and newly diagnosed asthma (26% and 33%). Half of the children with asthma of asthma selected breathing exercises (33%) for educational purposes (29%); every third child with BA of moderate severity was engaged in physical exercise, and most of the children with asthma severity did not have a hobby.

Conclusions: For children with bronchial asthma are characterized by psychological characteristics, depending on the severity of the disease. The following kinds of extracurricular activities / hobbies have the most favorable effect on the psychoemotional state of the child: breathing exercises, educational, music.

EFFECT OF NATURAL ASTAXANTHIN ON THE STATE OF LOCAL IMMUNITY OF ORAL TISSUES

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Acute traumatic lesions of the oral mucosa as a result of adaptation to removable dentures, lead to the formation of erosive and ulcerative lesions and, as a consequence, an inflammatory reaction. The universal protective and damaging system of the body, including inflammation, is a Pro-oxidant-antioxidant system. Natural astaxanthin, due to the feature of the biochemical structure, is the most powerful antioxidant that does not turn into a Pro-oxidant. It has a prolonged anti-inflammatory and immunomodulatory effect. We have proposed and developed an antioxidant gel based on natural astaxanthin for the prevention of acute trauma of the prosthetic bed with a partial secondary absence of teeth. The analysis of 105 patients was carried out, which were divided into three groups. Patients of group 1, consisting of 45 people aged 55–65 years, were given antioxidant gel with astaxanthin within 7 days after applying a partially removable prosthesis. Patients of group 2 in the number of 35 people aged 55–65 years preventive gel was not issued after the delivery of orthopedic design. Group 3 included 25 patients aged 35–45 years with no signs of inflammation of the oral mucosa. Group 3 preventive gel issued. In all groups assessed the state of local immunity of the oral cavity with the help of immunological studies for determining the concentration of CA in IgG, IgM by the method of radial immunodiffusion according to Mancini (REED) on the 4 stages of the study: before the study, after 7 days after imposing the partially-removable prosthesis, 21 days after the start of the study and on day 365. The studies showed an increase in local immunity of prosthetic bed tissues, which is confirmed by an increase in the content of immunoglobulins of class G in group 1 by 6 times. The content of immunoglobulin class M also increases within 7 days 2 times and retains the local immunomodulatory effect during the year in group 1. In group 2 and 3, local immunity remained unchanged. Astaxanthin has cytokine stimulating activity, acting as an immunomodulator. Analysis of the results of studies of B. Capelli and D. Tsisevski showed that the use of a small amount of astaxanthin increases the production of IgM, which is consistent with our data.

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ANALYSIS OF THE ASSOCIATION OF THE POLYMORPHISM A+1267G IN THE HSP70-2 GENE AND ITS EXPRESSION IN WOMEN WITH PROLONGED STRESS

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Introduction: Psychoemotional stress is currently seen as a potential risk factor for the development of cardiovascular pathology. One of the long-term stresses for a woman is a life-threatening illness of the child. Currently, the search for markers for the early detection of long-term stress complications is being carried out, and among them, the heat shock protein 70 is actively studied.

Aim: to investigate the features of expression of the HSP70 gene and the distribution of alleles and genotypes of the polymorphic marker A+1267G in women with prolonged stress. M***ethods:*** The main group consisted of 64 women – mothers of children with oncopathology, the average age was 35 (31–39) years. The average duration of stress was 7.3 (3–8) months. The control group included 60 women, comparable in age, without long-term stress. The assessment of the presence of stress was conducted according to the Hospital Alarm and Depression Scale (HADS). RNA and DNA were isolated from the leukocytes, (AmpliPraym RIBO-Sorb, ILS, RF) and a reverse transcription reaction was performed (OT-1, Sintol, RF). To determine the expression of the HSP70 gene, the droplet digital PCR method was used (Bio-Rad, USA). Detection of SNP HSP70-2 A+1267G was performed using the restriction PCR method (enzyme Pst1, SibEnzyme, RF). The results are processed in the program STATISTICA 10.

Results: In the main group severity of anxiety by HADS was 8.6 (6–11) points, in the control group – 5 (3–8) points ($p<0.05$). The level of depression in the main group was 7.7 (6–9) points, in the control group – 3.4 (1–5) points ($p<0.05$). In women with prolonged stress, a significant increase in the expression of the HSP70 gene was found in comparison with the control group ($p<0.001$). This group was heterogeneous in the profile of blood pressure: 10 women had BP episodes (group 1a), and 54 women had stable BP (group 1b). There was no difference in the expression of the HSP70 gene between these groups. At the same time, it was found that 80% of women in group 1a have the AA genotype of the polymorphic marker A +1267G in the HSP70-2 gene. ***Conclusions:*** In women with prolonged stress, an increase in the expression of the HSP70 gene in peripheral blood leukocytes was found in comparison with the control group. The genotype AA of the polymorphic marker A+1267G of the HSP70-2 gene can be considered as a possible predictor of the development of hypertension with prolonged stress.

VITAMIN D AND IMMUNE SYSTEM

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It is now clear that vitamin D has important roles in addition to its classic effects on calcium and bone homeostasis. As the vitamin D receptor is expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all are capable of synthesizing the active vitamin D metabolite, vitamin D has the capability of acting in an autocrine manner in a local immunologic milieu. Vitamin D is now recognized as an immunomodulatory. Vitamin D can modulate the innate and adaptive immune responses. According to the above-mentioned, at this stage the study aimed to find the relationship and the correlation between the deficiencies of vitamin D and immunological parameters of immune system. In the study have been involved 69 patients (among them 34 males and 35 females) of different ages, who were establish deficiencies of vitamin D in the S/R Institute of Allergology, Asthma and Clinical Immunology of Georgian Academy of Sciences for allegro-diagnostics (Tskaltubo, Georgia). On the ground of the aim the study included the following steps of diagnostics: I step: To detect the level of vitamin D in human serum and plasma by immunoassay (ELISA). II step: To measure the immunological parameters in blood by means of immuno-fluorescence (IgA,IgM, IgG;CD3 T-lymphocyte; CD4 T-helper cells; CD8 T –suppressors; CD16 NK cell; CD20 B-lymphocytes; CD45RA activated cytotoxic T-lymphocytes). For establishment corelation between parameters was studied r ratio of correlation. According to the analysis of the laboratory results allowed select the three groups of patients: I group: 21 (30.4%) patients with deficient of vitamin D (reference range <10 ng/ml); II group: 25 (36.2%) patients with insufficient of vitamin D (10–30 ng/ml); III (control) group: 23 (33.4%) patients with sufficient of vitamin D (30–100 ng/ml); In all 69 patient were not establish the intoxication level of vitamin D (>100 ng/ml). In patient from I and II group, different from III control group, were establish the low level the immune markers, such as: CD3 T-lymphocyte; CD4 T-helper cells; CD8 T –suppressors; CD16 NK cell. It was revealed high correlation between the levels of vitamin D and immune parameters: CD3 T-lymphocyte; CD4 T-helper cells; CD8 T-suppressors; CD16 NK cell (r=0,4–06); Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection. It is now clear that vitamin D has important roles in addition to its classic effects on calcium and bone homeostasis. As the vitamin D receptor is expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all are capable of synthesizing the active vitamin D metabolite, vitamin D has the capability of acting in an autocrine manner in a local immunologic milieu. Vitamin D can modulate the innate and adaptive immune responses. Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection. As immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D, the beneficial effects of supplementing vitamin D deficient individuals with autoimmune disease may extend beyond the effects on bone

International Journal on Immunorehabilitation
2019 Volume 21 No 1

and calcium homeostasis.The immune system defends the body from foreign, invading organisms, promoting protective immunity while maintaining tolerance to self. The implications of vitamin D deficiency on the immune system have become clearer in recent years and in the context of vitamin D deficiency, there appears to be an increased susceptibility to infection and a diathesis, in a genetically susceptible host to autoimmunity. The interest in this question is great. In this direction our research program is growing and progressive. *The publication has been prepared with the support of the «RUDN University Program 5-100».*

MOLECULAR, STRUCTURAL AND IMMUNOLOGICAL CHARACTERIZATION OF THE RECOMBINANT WILD-TYPE-LIKE VERSIONS OF THE MAJOR PARIETARIA ALLERGENS, PAR J 1 AND PAR J 2

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Parietaria judaica is one the most common pollen allergen sources in the Mediterranean area. Par j 1 and Par j 2, the major Parietaria allergens, belong to the family of lipid-transfer proteins. The aim of this study was to express and purify correctly folded recombinant Par j 1 and Par j 2 molecules which would mimic the structural and immunological features of the natural allergens. We compared the recombinant Par j 2 (BvPar j 2) and Par j 1 (BvPar j 1) obtained by expression using baculovirus infected insect cells and Par j 2 expressed in bacterial expression system using *Escherichia coli* cells (EcPar j 2). Analysis by CD showed that BvPar j 2 and BvPar j 1 assumed mainly α-helical structure whereas EcPar j 2 contained mainly unordered species. IgE reactivity of the EcPar j 2 and BvPar j 2 proteins was tested using sera from 27 Parietaria allergics. BvPar j 2 showed significantly higher IgE reactivity than EcPar j 2. Rat basophil leukemia cells transfected with human FceRI receptor were used to compare the allergenic activity of various concentrations of BvPar j 1, BvPar j 2 and EcPar j 2 in terms of their capability to induce mediator release in 9 allergic donors. The data demonstrated that all three recombinants show allergenic activity and are capable to induce basophil degranulation. However, BvPar j 2 is potent already in 100-fold lower concentration than EcPar j 2. To find the capability of BvPar j 1 and BvPar j 2 to inhibit IgE binding of allergic patients to *Parietaria judaica* pollen extract we tested sera of 9 allergics in ELISA inhibition. We have seen a significant prevalence in inhibition potency of BvPar j 2 over BvPar j 1. This study shows that IgE recognition of the main allergen of Parietaria judaica pollen requires conformational epitopes. By the eukaryotic expression of Par j 1 and Par j 2 in insect cells it was possible to obtain folded recombinant proteins with superior IgE reactivity over E. coli expressed Par j 2. BvPar j 1 and BvPar j 2 can now be used for IgE-based diagnostic testing for identifying Parietaria allergic patients. Furthermore, RBL assay and inhibition experiments widen the overview of significance of the major Parietaria allergens. These findings can be important for the development of allergen-specific treatment.

CONTENTS

Volume 21 No 1 2019

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