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ASSESSMENT OF IMMUNOLOGICAL DISORDERS IN THE GENESIS OF BRONCHIAL ASTHMA IN CHILDREN WITH DIFFERENT DEGREES OF THE DISEASE CONTROLLABILITY

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It is established that children with bronchial asthma may have pronounced changes in their immunological status, concerning both its cell and humoral components, and to a significant extent they are determined by the disease severity. In the examined patients with bronchial asthma, a limited reserve of phagocytic cells and their phagocytic activity have been established. The maximum inhibition of phagocytosis was observed in patients with uncontrolled bronchial asthma ($p < 0.05$). At the same time, in patients with uncontrolled and partially controlled bronchial asthma, a reduction of their regulatory index was registered, which was caused by the reduction of CD4+ portion and the increase of CD8+ content ($p < 0.05$). Manifestation of a positive highest degree correlation ($r=0.79$, $p<0.05$) between the blood serum IL-6 content and the BA course severity in children.

Key words: bronchial asthma, children, immunity.

The work is a fragment of the research project "Development of methods for prediction, treatment and rehabilitation of widespread somatic and surgical pathology in children in modern environmental conditions", state registration No. 0114U005518).

Allergic diseases are among the public health indicators that are regulated by the WHO Regional Office for Europe under the Health for All strategy. The increase in the prevalence of bronchial asthma (BA), which is one of the most frequent and severe allergic diseases in the population, including children, indicates the need for further fundamental studies on the mechanisms of pathogenesis, and on this basis the development of new treatment and prevention programs for the disease control.

Today, as defined by GINA (2016), asthma is considered as a chronic inflammatory disease of the respiratory tract, in the pathogenesis of which a large number of cells and cellular elements is involved. The latter include, first of all, factors of nonspecific (innate) immunity: mononuclear phagocytes (monocytes, tissue macrophages) and granulocytes (neutrophils, eosinophils, basophils of peripheral blood and tissue) [1, 2].

Nevertheless, it is established that in BA there are changes in different components of the immune system (T and B lymphocytes, phagocytic cells, natural killers), activation of specific and enzymatic processes is noted, reactions to pathologically altered lung tissue develop. At the same time, there is an increase in the content of circulating immune complexes (CIC), the level of both general and specific Ig E increases, the level of sIg A decreases, which is caused by pathological changes of the respiratory tract mucous membrane and by alteration of the epithelium [3, 4].

Development of asthma is associated with various disorders of the quantitative and functional status of the immune system [5, 6]. Thus, it has been shown that the morpho-functional changes that are associated with chronic inflammatory process in the tracheobronchial tree in BA are due to the disruption of complex regulatory responses between bronchial cells and the immune system with cytokine involvement at the local and systemic levels.

The intensity of these changes in the immune system, their directivity and the possibility of combinations in children BA are extremely variable and depend on the influence of various factors, namely: the severity of intoxication and antigenemia, the level of biologically active substances, blocking complexes, C-reactive protein, stress etc. [7, 8].

The purpose of the study was to determine the immunological features in BA children with varying degrees of the disease controllability.

Materials and methods. The total of 87 children aged 10 to 18 years with bronchial asthma who were treated in the allergic department at the CSTO of Ivano-Frankivsk were examined. The diagnosis was verified in compliance with the Protocol for the diagnosis and treatment of asthma in children (No. 868 of 08.10.2013). According to the results of the asthma test for the level of the disease controllability, the children were distributed as follows: 27 (31.0%) - controlled (CBA), 38 (44.0%) - partially controlled (PCBA), and 22 (25.0%) - with uncontrolled bronchial asthma (UCBA). The control group consisted of 20 healthy children of the same age.

State of the nonspecific body resistance was studied by determining the indices of phagocytosis (in compliance with the method of I.V. Petrov et al., 1984): phagocytic index (PI), phagocytic number (PN) in neutrophilic granulocytes.

Oxygen-dependent metabolic activity of neutrophils was determined by the reduction of nitroblue tetrazolium (NBT test) (by B. Park method in the modification of M.E. Vicksman, M.M. Maysky, 1982). A spontaneous and zamozine-stimulated test was performed with the calculation of NBT-positive neutrophils (N, %) and neutrophil activation index (IA, units).

A comprehensive immunological examination included the study of mature T-lymphocytes (CD3+) and their subpopulations (CD4+, CD8+, CD16+), as well as B-lymphocytes (CD22+) by conventional methods using the erythrocyte rosette formation test, using kits of erythrocyte diagnostics (produced by TOV NVL "Granul", Kharkiv).

To assess the B-component of the immune system the content of Ig class G, M, A (Manchini et al., 1965) was studied. The IgE content was determined by means of enzyme immunoassay.

The CIC concentration in the blood serum was studied by the precipitation method with subsequent photometry.

Serum cytokine content (IL-6, IL-4) was determined by enzyme-linked immunosorbent assay with a "STAT-Fax 303 Plus" apparatus (USA) using test systems manufactured by "Diaclone" (France) in compliance with the manufacturer's instructions.

The obtained study results were processed using the "MedStat" software (Ukraine) using descriptive statistics and correlation analysis methods.

Results of the study and their discussion. In the course of the study it was found that the development and course of asthma in children is accompanied by changes in their immunological status. The nature of the immunological changes and their severity were largely determined by the degree of the disease controllability.

In particular, patients with UCBA experienced significant changes in the neutrophils phagocytic activity, manifested by the lowest possible number of cells capable of phagocytosis and by a decrease in their phagocytic capacity. At the same time, the PI and PN indices in the UCBA patients surveyed, accounting for (28.1±1.1)% and (3.5±0.9) relative units (RU), respectively, were reliably lower than those in healthy children (pH <0.05), but similar in children with higher controllable disease (p <0.05) (table 1).

Table 1

Indices of phagocytosis status in healthy persons and patients with bronchial asthma of varying controllability (M±m)

Indices	UCBA(n=22)	PCBA (n=38)	CBA (n=27)	Healthy (n=10)
PI, %	28.1±1.1*◊^	47.1±0.9*^ Δ	78.3±1.2◊ Δ	64.8±1.8
PN, ум. од.	3.5±0.9*◊	4.2±0.08* Δ	6.8±0.09*◊ Δ	7.5±0.06
NBT spontaneous:				
- IA, RU	0.09±0.01*◊	0.10±0.01	0.12±0.01*◊	0.15±0.02
- N, %	8.0±0.01*^	9.0±0.01*^	11.1±0.01*	12.0±0.07
NBT stimulated:				
- IA, RU	0.7±0.01*^◊	1.2±0.01^	2.0±0.03*◊	1.2±0.02
- N, %	41.3±0.01*^◊	52.4±0.06*^	97.2±0.08*◊	76.3±0.5

Notes: 1. * - difference reliability compared to healthy (p<0.05); 2. ^ - difference reliability between indices in patients with UCBA and PCBA (p<0.05); 3. ◊ - difference reliability between indices in patients with із UCBA та CBA (p<0.05); 4. Δ - difference reliability between indices in patients with PCBA та CBA (p<0.05).

The opposite is the situation with regard to the factors of nonspecific protection in children with CBA. Thus, the increase of PI (%) in children with CBA was almost indistinguishable from that in the control group; the PN was lower than that in healthy subjects (p_N <0.05), but reliably higher than the similar index in children with UCBA and PCBA (p <0.05).

In children with PCBA, the vector of phagocytosis disorders tendency was shifted toward deficiency. The percentage of phagocytic cells was significantly reduced compared to the healthy group (P_N<0.05), although the PN was greater than that of children with UCBA, but significantly lower than that of the healthy (P_N<0.05) and patients with CBA (p <0.05).

Indices of spontaneous NBT test revealed insufficient degree of the phagocytic cells irritation and their low killing ability in patients with UCBA (P_N<0.05). In the other groups surveyed, the changes were less significant.

The stimulated NBT test showed low potential activity of phagocytic cells and the completion of phagocytosis in children with UCBA compared to those in healthy (p <0.05) and children with CBA (p <0.05) groups. In children with PCBA, the IA (RU) and N (%) rates were higher than those of the UCBA (p <0.05), but significantly lower than in children with PCBA (p <0.05) and healthy ones (P_N <0.05). Oxygen-dependent neutrophil microbicidal activity was found to be maximally increased in children with

CBA (p <0.05), which suggests that there is a correlation between neutrophil granulocytes activation and the manifestation of chronic inflammatory process in the respiratory tract inherent of BA.

Thus, in patients with BA, there are pronounced changes in the nonspecific body resistance, which are manifested, first of all, by the limitation of the phagocytic cells reserve and their phagocytic activity. The most pronounced inhibition of phagocytosis was observed in patients with UCBA, while in patients with CBA the phagocytic activity tended to increase. Therefore, it can be argued that at the beginning of the chronic inflammatory process development in the bronchi the phagocytic activity grows and decreases sharply as the chronicity of inflammatory changes in the bronchial tree increases and the severity of the asthma course grows. That is, in the case of severe uncontrolled course of asthma there is a more pronounced manifestation of the inflammatory process, which correlates with a number of studies.

Верифіковано дисбаланс клітинної ланки імунітету у пацієнтів із усіма варіантами БА у гострому періоді захворювання (табл.2).

The imbalance of the immunity cellular component in patients with all BA variants in the acute period of the disease was verified (table 2).

Table 2

Indices of cellular and humoral immunity in healthy children and those with bronchial asthma depending on its controllability (M±m)

Indices	UCBA(n=22)	PCBA (n=38)	CBA (n=27)	Healthy (n=10)
CD3+,%	41.1±0.44*^◊	44.1±0.37*^	60.3±0.46*◊ Δ	63.8±0.63
CD4+,%	29.4±0.72*^◊	38.1±0.54*^	41.8±0.61*◊	45.5±0.73
CD8+,%	43.2±0.68*^◊	39.5 ±0.45^ Δ	25.6 ±0.69◊ Δ	28.7±1.09
IPI (CD4+/ CD8+)	0.87±0.05*◊	0.97±0.02*	1.96±0.03◊ Δ	1.98±0.12
CD16+,%	19.7±0.22*^◊	22.4±0.31*^ Δ	26.9±0.44◊ Δ	27.7±0.61
CD22+,%	52.8±2.7*^◊	43.9 ±3.6*^ Δ	39.8 ±3.1*◊ Δ	21.7±2.90
Ig G, g/l	14.1±0.22*^◊	12.6±0.15*^	10.9±0.3◊	9.71±0.27
Ig A, g/l	0.87±0.05*	0.9±0.02*	0.9±0.03*	1.3±0.10
Ig M, g/l	2.8±0.12*◊	2.6±0.07*	1.9±0.13◊	1.7±0.09
Ig E, IU/ml	389.7±3.13*^◊	246.7±1.46*^ Δ	198.0±1.24*◊ Δ	29.3±1.40
CIC, RU	62.9±0.69*◊	53.1±0.91* Δ	44.6±0.83*◊ Δ	40.1±1.04

Notes: 1. * - difference reliability compared to healthy (p<0.05); 2. ^ - difference reliability between indices in patients with UCBA and PCBA (p<0.05); 3. ◊ - difference reliability between indices in patients with із UCBA та CBA (p<0.05); 4. Δ - difference reliability between indices in patients with PCBA та CBA (p<0.05).

Thus, in patients with CBA, changes in the cellular immunity component were manifested by a slight decrease in the content of total T lymphocytes (CD3+), which was mainly due to a decrease in the number of T cells with CD8+ phenotype and the tendency to increasing absolute and relative content of CD22+ cells in the blood. Obviously, the absence of changes in the CD4+ fraction in patients with CBA is explained by the redistribution of Th toward the pool of Th 2 cells, which determines the immune response in BA.

In patients with PCBA and UCBA the total T-lymphocyte (CD3+) content did not differ significantly between them, but it was reliably higher than in patients with CBA (p <0.05). At the same time, patients with UCBA showed a significant decrease in CD4+ lymphocytes compared to those with higher controllability of the disease (p <0.05), and their level of cytotoxic suppressors was by 1.4 times higher than CD8 + in patients with PCBA and by 1.8. – than in those with CBA (p <0.05). At the same time, in patients with UCBA and PCBA a significant decrease in the regulatory index was registered due to a decrease in the CD4+ fraction and an increase in the CD8+ content (p <0.05). The decreased content of T lymphocytes in the blood in BA may be due to the accumulation of these cells in the respiratory tract and is a predictor of inflammation in the bronchi.

When analyzing the level of lymphocytes with the CD16+ phenotype, the major part of which is represented by natural killer cells, in children with UCBA this index was reliably lower compared to that in the control group (P_N <0.05). In children with PCBA and CBA the CD16+ content was lower compared to that in the control group, but the difference was not reliable in children with CBA.

Despite the heterogeneity of the groups in terms of the BA severity, the nature of the humoral immune system's response had common tendencies, and differences were only observed in the intensity of the reaction processes. Thus, in children with UCBA the number of lymphocytes with the CD22+ phenotype was high and amounted to 52.8%, in patients with PCBA - 43.9% and in children with CBA - 39.8%. At the same time, the increase of CD22+ cells (p <0.05) in patients with UCBA and PCBA was characterized by a decrease of CD3+ content by 1.5 and 1.2 times, respectively, and the decrease in CD8+

exceeded the decrease in CD4+ cells with the formation of a relative suppressor variant. secondary immune response, which is a common phenomenon in chronic respiratory diseases.

With regard to the total CIC content, its highest values are verified in patients with UCBA, slightly lower in PCBA. Thus, they exceeded the reference value by 2.1 and 1.7 times, respectively (P_N <0.05). In patients with CBA, the CIC content did not virtually differ from that in healthy persons. The data obtained may indicate a significant role of the immunocomplex component in the pathogenesis of BA with a low degree of controllability.

Quantitative disorders of the regulatory part of the humoral link have been largely reflected in the synthesis of different classes immunoglobulins. An inadequate, probably compensatory, statistically significant difference in providing children with Ig E was revealed, which consists in its overproduction in comparison with healthy ones. At the same time, its concentration exceeded the normal values in children with all variants of BA and was maximal in children with UCBA (P_N <0.05).

Analysis of the major immunoglobulins classes showed that patients with BA were characterized by an increase in the level of total Ig G and Ig M (P_N <0.05), with a simultaneous decrease in Ig A level (P_N <0.05). The most pronounced deviations from the normal values of these indices were in patients with UCBA, but they were not reliably different from the respective values in patients with higher levels of the disease controllability.

An increase in the IgE and IgG content in patients with BA indicates the functional tension of B lymphocytes. This reaction of the immune system reflects the severity of the systemic immune response to the inflammatory response in the body of patients and progresses with increasing severity of the disease. Increasing IgG levels, in turn, can contribute to the formation of excessive CIC.

The study found that all patients with BA have an imbalance in the cytokine status, which is largely determined by the degree of the disease controllability (table 3).

Table 3

The content of cytokines in the blood serum of healthy and children with different levels of BA controllability (M±m)

Index. pg/ml	UCBA[1] (n= 22)	PCBA [2] (n=38)	CBA [3] (n=27)	P^{1-2}	P^{1-3}	P^{2-3}	Healthy (n=10)
IL-6	25.49±1.54	13.72±0.34	5.30±0.23	* ^	* ^	*	3.59±0.11
IL-4	21.21±0.55	18.45±0.28	11.46±0.39		* ^	*	11.15±0.84

Notes: 1. * - difference reliability compared to healthy children (p<0.05); 2. ^ - difference reliability between indices in patients with different levels of БА controllability(p<0.05)

Thus, a significant (P_N <0.05) IL-6 content increase in the blood serum was observed in patients with CBA with the IL-4 level preserved.

A significant increase in IL-6 levels was observed in patients suffering from PCBA compared to the healthy group (P_N <0.05) and patients with CDA (p <0.05), with the simultaneous significant decrease in the blood serum IL-4 level (P_N <0.05).

In patients with UCBA, the IL-6 content was elevated compared to the normal (P_N <0.05), but slightly different from those of PCBA patients, which, in our opinion, is due to the administration of higher doses of inhaled glucocorticosteroid drugs, as well as to the depletion of immune inflammation mechanisms in this category of patients. At the same time, the level of IL-4 in children with UCBA, being (21.05±0.27) pg/ml, probably exceeded not only the similar index in healthy (P_N <0.05), but also that in children with CBA (p <0.05). Such changes indicate a high intensity of the inflammatory process, with simultaneous pronounced sensitization of the body and the intensity of nonspecific protection factors in children with UCBA.

High degree positive correlation (r = 0.79, p <0.05) was found between the blood serum IL-6 content with BA severity in children.

Thus, the increased content of proinflammatory while maintaining the level of anti-inflammatory cytokines in the blood serum of patients with CBA reflects the initial inflammatory changes in the bronchial tree, when the mucous membrane has not completely lost its protective properties, there is no permanent persistence of bacterial infection.

In children with PCBA, activation of proinflammatory cytokines may be associated with a predominantly prolonged persistence of bacterial infection and relatively more frequent exacerbations of viral-bacterial etiology, it can also testify to depletion of the cytokine-producing capacity of the producing cells. At the same time, the decrease of IL-4 content in children with PCBA may indicate a depletion of the compensatory anti-inflammatory mechanisms of the immune system and insufficient anti-inflammatory response.

The maximum blood serum IL-4 level that occurs in UCBA is a manifestation of a pronounced allergic component in the pathogenesis of the disease in this category of patients and indicates a Th2 mechanism of the allergic reaction and inflammation that redirect the synthesis of IgG and IgM in B-lymphocytes to the IgE synthesis, and thus significantly affects the BA severity. At the same time, a probable increase in the level of proinflammatory cytokine (IL-6) in children with UCBA leads to the induction of other proinflammatory cytokines synthesis, including TNF-α, and determines the degree and severity of the inflammatory process, namely the development of its proliferative stage, and processes of the bronchi remodeling. Thus, the most pronounced changes in the cytokine status of patients with UCBA are determined by the multifactorial genesis of this clinical form and determine the severity of clinical symptoms and the degree of resistance to therapy in such patients.

Thus, the variant and severity of immunological shifts in patients with BA are strictly determined by the degree of disease controllability. Thus, in children with UCBA, a decrease in the functional capacity of natural killers, hyperproduction of IgE and IgG with simultaneous imbalance of the phagocytic link is observed against the background of reduction in the total number of T lymphocytes (mainly CD3+ and CD4+). In children with PCBA, a decrease in most components of the T-cell subpopulation (excluding CD8+) is determined against the background of pronounced hyperimmunoglobulinemia and limitation of the phagocytic function. Hyperimmunoglobulinemia was predominant in CBA patients with relatively normal indices of the phagocytic system's components.

The heterogeneity of fluctuations in indices within a single component of the immune system in children with varying degrees of BA controllability may be due to adaptive functional abilities that form individual adaptive responses and permanent functional readiness for different antigen load.

Conclusions

1. In BA, the following changes in the immune status are typical of the child: a decrease in the number and functional status of T-lymphocytes, dysfunction of B-lymphocytes (increase in the number of B-cells, decrease in their functional activity), disimmunoglobulinemia (increase in the IgG, IgE content with simultaneous reduction of IgA), increasing content of CIC, reduction of natural and increase of the specific antibodies level, reduced number of NBT-positive neutrophils and their functional activity.

2. The level of immunological changes in children with BA can serve as a marker of systemic cellular metabolism disturbance and is strictly determined by the nosology severity.

Prospects for further research *are to study the possibility of drug correction for immunological shifts in children with bronchial asthma.*

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Реферати

ОЦІНКА ІМУНОЛОГІЧНИХ ПОРУШЕНЬ У ГЕНЕЗІ БРОНХІАЛЬНОЇ АСТМИ РІЗНОГО СТУПЕНЯ КОНТРОЛЬОВАНОСТІ У ДІТЕЙ

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Встановлено, що у дітей із бронхіальною астмою мають місце виражені зміни в імунологічному статусі, що торкаються як клітинної, так і гуморальної його ланок та в значній мірі визначаються ступенем тяжкості захворювання. У обстежених із бронхіальною астмою встановлено обмеження резерву фагоцитуючих клітин та їх фагоцитарної активності. Максимально виражене пригнічення фагоцитозу відмічалося у обстежених із

ОЦЕНКА ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ В ГЕНЕЗЕ БРОНХИАЛЬНОЙ АСТМЫ РАЗНОЙ СТЕПЕНИ КОНТРОЛИРОВАННОСТИ У ДЕТЕЙ

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Установлено, что у детей с бронхиальной астмой имеют место выраженные изменения в иммунологическом статусе, что касается как клеточного, так и гуморального звеньев и в значительной мере выражаются степенью тяжести заболевания. У обследованных с бронхиальной астмой установлено ограничения резерва фагоцитирующих клеток и их фагоцитарной активности. Максимально выраженное угнетение фагоцитоза наблюдалось у обследованных с

неконтрольованою бронхіальною астмою (p<0,05). Одночасно у пацієнтів із неконтрольованою та частково контрольованою бронхіальною астмою реєструвалось вірогідне зниження регуляторного індекса, зумовленого зменшенням частки CD4+ та зростанням вмісту CD8+ (p<0,05). Встановлено наявність позитиваного кореляційного зв'язку високого ступеня (r=0,79, p<0,05) між вмістом в сироватці крові IL-6 із тяжкістю перебігу БА у дітей.

Ключові слова: бронхіальна астма, діти, імунітет.

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неконтролированной бронхиальной астмой (p<0,05). Одновременно у пациентов с неконтролированной и частично контролированной бронхиальной астмой регистрировалось достоверное снижение регуляторного индекса, выражавшегося уменьшением процента CD4+ и увеличением CD8+ (p<0,05). Установлено наличие положительной корреляционной связи высокой степени (r=0,79, p<0,05) между содержанием в сыворотке крови IL-6 и тяжестью течения бронхиальной астмы у детей.

Ключевые слова: бронхиальная астма, дети, иммунитет.

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PECULIARITIES OF TLR9 EXPRESSION ON IMMUNE COMPETENT CELLS IN REACTIVE ARTHRITIS PATIENTS WITH CHRONIC EPSTEIN-BARR VIRUS INFECTION

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The work presents the study findings on the TLR9 expression in immune competent cells in reactive arthritis patients with chronic Epstein-Barr virus infection, and considers the possibility of the reactive arthritis transformation into rheumatoid arthritis. It was established that expression of TLR9+CD123+ on monocytes was reliably higher in the blood of reactive arthritis patients as compared to healthy individuals, while in patients in active phase of EBV-infection the expression of this receptor was reliably higher as compared to similar indices of patients at the latent phase. At that, the number of TLR9+CD123+-monocytes in patients with reactive and rheumatoid arthritis was not reliably different. The number of TLR9+CD123+-lymphocytes as compared to indices of healthy individuals was reliably higher in patients with rheumatoid arthritis at both phases of chronic EBV-infection, while in patients with reactive arthritis it was only characteristic at the active phase of the infection. Expression of this receptor on lymphocytes turned out to be reliably higher in patients with rheumatoid arthritis as compared to patients with reactive arthritis, particularly at the active phase of chronic EBV infection.

Key words: reactive arthritis , rheumatoid arthritis, chronic Epstein-Barr Virus Infection, TLR9.

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Over the last years, there has been a wide spread of reactive arthritis cases (ReA), especially among young people. The relevance of the problem of ReA is attributed to its high incidence and difficult differential diagnostics [14]. It is very often the case when clinically similar joint problems could be initial signs of systemic diseases. Currently, ReA is treated as a multifactor joint disease which belongs to the group of seronegative spondilo-arthropathies HLA-B27-associated that develop due to immune disorders after having the urogenital, intestinal, respiratory, and tonsilogenic infections. Today, dependency of the incidence of contraction of the ReA on the type of the pathogen has been well studied, however, there is no clear answer to the question why different micro-organisms can cause ReA, or cause it with different incidence. Currently, special focus in the development of ReA is allocated to the role of viruses, including also the chronic Epstein-Barr virus (EBV) [4]. EBV infection is one of the most widespread infections in the world. In the recent years, during primary introduction of infection, the virus has often caused blurred atypical forms of disease with rapid chronization. EBV persists lifelong in the human body due to its ability to suppress effector mechanisms of immune competent cells [3]. One of the theories on complications in ReA development is about its transformation into rheumatoid arthritis (RA). RA is an autoimmune disease characterized with chronic inflammation of joints that will gradually result in damage of cartilages and bones; it is characterized with synovial hyperplasia with massive infiltration of inflamed cells. Immune cells play a key role in RA progression due to production of pro-inflammatory cytokines [1]. One of the causing factors for the transformation could be Herpesviruses.

A conducting system providing for recognition of infections, and viruses in particular, is a system of Toll-like receptors (TLRs), and more specifically TLR9 [12]**.** The TLR9 is an important intracellular receptor expressed on immune competent cells; it mostly binds the DNA that is present in viruses; it launches signal cascades that lead to pro-inflammatory response of cytokines [4]. It has been found a different interaction of EBV with TLRs expressed on different cells [9].