УДК 616.988.55-058.8-07

CLINICAL AND IMMUNOLOGICAL ASPECTS OF INFECTIOUS MONONUCLEOSIS

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The pathogen of infectious mononucleosis (IM) is the Epstein-Barr virus (EBV) that belongs to Herpesviridae family. The severity of disease course varies in a wide range, which is caused by the variety of combinations of different individual features of the organism immune reactions with a wide specter of possible influence of EBV on the immune system [1-7]. The main elements of the latter are the ability to influence substantially on he functional state of both the infected and intact immune cells of different populations, to modulate the expression level of genes, that are responsible for cytokine synthesis, to regulate the cell proliferative activity and apoptosis, etc [8-11]. The polyclonal activation of infected B-lymphocytes (in vitro this population under the influence of EBV infection immortalizes, i.e. acquires the features of tumor transformation) is accompanied by increase in sensibilization to different antigens, causes reactive functional an quantitative changes in T-cell population, that can be found both in blood and lymphoid organs. [12-15]. The result of these processes is the activation of cell cytotoxicity that, from one side, allows the organism to control the B lymphocyte proliferation and to destroy the infected cells, from the other it is the cause of the majority of IM clinical symptoms. [12], [16-18]. According to the modern concept, IM is the self-limiting lymphoproliferative syndrome that is characterized by polyclonal B-lymphocyte activation due to infection, and reactive T lymphocyte proliferation and activation [13, 19].

Taking into the consideration the described above data, we have aimed to study the clinical and immunological aspects of IM with different severity of disease clinical manifestations in order to improve the immunorehabilitation of IM patients and, therefore, to increase the efficacy of the existing therapeutic schemes.

Materials and methods

The object of the study was 110 IM patients with different disease severity, hospitalized for investigation in Kharkov Regional Isolation Hospital in the period 2005 – 2007 years. In course of the study 50,90 % women (56 patients) and 49,10 % men (54 patients) were examined. The men/women ratio was about 1:1. The mild age of examined patients was 24±5 years. The examined patients were divided in two groups. The first group consisted of 56 patients with minor disease severity, the second group – of 54 patients with mild disease severity. The disease severity criteria were the intensity of the main syndromes (intoxication, lymphoproliferative, nasopharyngeal, hepatolienal, hemophagocytic), the disease course duration, the presence and the character of complications. All 110 patients were observed both in the acute and in the reconvalescence phase of the disease. The control group consisted of 22 practically healthy individuals that correlated with the study groups by age and sex.

The etiologic diagnostics of the disease was carried out with the help of identification of specific anti-EBV antibodies - IgM and IgG to the early antigen (EA), virus capside antigen (VCA) and EBV nuclear antigen in blood serum with the help of immunosorbent assay "Vector-Best " (Russia).

The laboratory diagnostics of EBV infection was based on the hematological changes in peripheral blood. The leukocyte formula was determined in the unquentums, colored by Romanovsky-Gimsa method. The isolation of mononuclear cells from blood with heparin was carried out according to standard method (Vozit, 1974) in Ficoll-verographine density gradient 1,077 (Sigma, USA).

Lymphocyte phenotype was studied by immunofluorescence with the use of monoclonal antibodies to differential antigens CD3, CD4, CD8, CD16, CD19. Serum concentrations of immunoglobulins IgM, IgG, IgA were determined by radial immunodiffuse method by Manchini with monoreceptor serums («Medgamal», Moscow) in agarose gel (Difco, USA). The reaction of blastocyte transformation of lymphocytes with non-specific mitogen (RBTL with FGA) was carried out with the help of morphologic method. Blood cytokine concentrations and levels of IgE and IgG were determined with immunosorbent test assays "Vector-Best (Russia)". Circulating immune complexes were determined with standard precipitation method with 3, 5% polyethylene glycol solution (м.м.6000) (AppliChem Gmb) and further spectrometry, according to optical density values.

Results and discussion

The EBNA and EA antigens determination, and also determination of IgM to VCA was considered to provide enough information for diagnosis of infection and establishment of the disease stage. [2, 3, 20].

In all examined patients high levels of IgM to VCA in acute phase were determined, in convalescence phase high levels of IgG to EBNA and EA were found, independently of clinical manifestations state. In control group in 72% IgG to EBNA was found.

In IM diagnostics hemogram plays an important role, as in course of the disease leukocytosis with the shift to the right of the white blood parameters due to the lymphomonocytosis and presence of atypical mononuclear cells. For IM diagnosis verification along with the clinical picture the isolation of 10-20% mononuclear cells is considered enough, as the lesser quantity is isolated in other virus infections as well. There is an assumption that atypical mononuclear cells in IM are transformed T-lymphocytes, but their origin is not finally established [1, 2, 21].

We have analyzed leukograms of IM patients in different severity stages of disease: in acute phase and in early reconvalescence phase (110 patients in both groups, as all patients have undergone both disease stages). The research results are represented in table 1.

Table 1. The leukogram parameters and relative content of circulating lymphocyte populations in patients with different severity stages of IM.

Parameters		First group (minor severity) (n= 56)		Second group (mild severity) (n= 54)		Control group (n=22)
		Acute phase	Early reconvales cence phase	Acute phase	Early reconvales cence phase	
General leukocyte quantity (x 10^9/l)	M	8,7	8,15	13,9	8,9	6,9
	m	±0,9[1]	±0,7[1]	±2,02[1,2]	±0,9[1]	±0,8
Monocytes (%)	M	6,4	7,8	8,3	11,2	5,3
	m	±0,8	±0,9	±0,9[1]	±1,1	±0,7
Lymphocytes (%)	M	52,1	42,8	69,3	52,1	26,1
	m	±2,3[1]	±3,7[1]	±2,9[1,2]	±1,8[1]	±1,8
Atypical mononuclear cells (%)	M	12,3	7,3	18,1	10,6	-
	m	±0,9[1]	±1,5[1]	±1,4[1,2]	±1,8[1,2]	-

Notes:

1. Data differ reliably (p<0,05) from control group

2. Data differ reliably (p<0,05) from group with minor disease severity

In IM acute stage in patients with disease course of mild severity the general lymphocytes rate was reliably higher than in patients with mild disease severity. Compared to the control, their quantity was reliably higher in both study groups. The increase in lymphocyte quantity in acute phase ranged from (62,1±2,3) % in minor disease severity up to (69,3±2,9) % - in mild disease severity. The relative quantity of stab, segmentonuclear neutrophils and eosinophils did not have significant differences. The quantity of monocytes increased in the beginning of reconvalescence period, along with decrease in general quantity of lymphocytes.

In IM acute phase the relative quantity of atypical mononuclear cells in IM patients with mild disease severity (18, 1±1, 4)[2] was reliably higher than in minor disease severity (12,3±0,9)[1]. In 26,36 % (29 patients) the appearance of atypical mononuclear cells was delayed, they appeared on the second and third week after the onset of disease, which has significantly complicated the diagnostics. Atypical mononuclear cells were preserved sufficiently long. In early convalescence period in both study groups their quantity decreased gradually alongside with decrease in general lymphocytosis.

Therefore, there is a direct dependence between the IM disease severity and changes in leukogram (general leukocytosis due to lymphomonocytosis and atypical mononuclear cells quantity).

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As it is known, the most marked changes under the influence of EBV are found in immune system [1, 2, 7]. The effective immune response on the EBV infection includes the humoral and cellular components.

We have carried out the analysis of the dynamics of immune response parameters in patients with different stages of IM. The research results are also represented in table 2.

In the first group of patients (with minor IM severity) cytotoxic lymphocyte levels CD_8, natural killer cells CD_{16} and B-lymphocytes CD_{19} did not differ significantly from control.

Lymphocyte phenotyping has revealed significant differences in acute IM between study groups in levels of CD_8, CD_{16}, CD_{19} in blood, and in CD_3 and CD_4 blood levels no significant differences were found.

Along with the increase in clinical IM exacerbations the CD_{19} B lymphocytes percent in blood increase, and, on the contrary, the quantity of cytotoxic lymphocytes decreased (CD_8 and CD_{16}).

In disease dynamics the normalization of the absolute and relative parameters of CD_4, CD_8 and CD_{19} was slow and in 43,64 % - 48 patients in reconvalescence period remained changed. In patients with minor disease severity normalization of these parameters was quicker

than, in patients with mild disease severity, and already in early reconvalescence period these parameters were near control values.

Different severity of clinical symptoms was also associated with significant features of the non-specific component of immune response that were evaluated according to the indirect and humoral immunity parameters.

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The known specificity of the B lymphocyte injury by EBV and effect of infection on their involvement in proliferation with damaged antibody production of heterophyle, anti-thrombocyte and other antibodies.

The immunoglobulin levels study in IM has shown the polyclonal nature of their synthesis activation in the acute phase of the disease. Inadequate immune response contributes to the development of non-specific immune reactions in the organism, and, in consequence, in patients' blood serum a significant quantity of heteroantibodies is found. Great quantity of B-lymphocytes, damage of antibody production, presence of circulating immune complexes are, possibly, connected with damage of the B-lymphocytes by persisting EBV.

The results of humoral immunity state are represented in table 2.

In acute phase the IgM level in patients with minor disease severity was higher that the same parameter in control group, IgG, IgA, IgE levels did not vary significantly from control. Humoral branch of immune response in IM patients with mild disease severity was more expressive, it is confirmed by activation of IgM, IgA and, in particular, IgE synthesis. No significant differences from control group in IgG level was observed.

In patients with mild disease severity in acute phaseT lymphocytes have shown decreased capability to proliferation under the influence of FGA. The amplified circulating complexes accumulation also attracts attention, as well as the significantly increased general IgE in this patient group. Such increased values are preserved in early reconvalescence period. In minor disease severity the levels of these parameters did not vary from control ones.

Table 2.Cellular and humoral immunity in IM patients with different disease severity and development stage.

Parameters		First group (minor severity) n=56		Second group (mild severity) n=54		Control group (n=22)
		Acute phase	Early reconvalescence phase	Acute phase	Early reconvalescence phase	
CD_3 (%)	M	67,0	62,4	63,8	68,5	61,4
	m	±2,2	±2,8	±1,7	±2,0[1]	±1,2
CD_4 (%)	M	41,7	38,3	44,4	41,5	40,5
	m	±2,1	±2,0	±1,9	±2,7	±1,5
CD_8 (%)	M	23,4	24,4	15,9	15,2	20,7
	m	±1,8	±1,9	±1,9[1,2]	±1,2[1,2]	±1,3
CD_{16} (%)	M	15,8	16,1	10,7	15,2	16,0
	m	±1,9	±1,2	±1,9[1,2]	±1,3	±1,1
CD_{19} (%)	M	13,8	13,0	20,4	17,6	12,5
	m	±1,8	±1,6	±1,9[1,2]	±1,7[1,2]	±2,1
IgM (g/l)	M	2,1	1,9	2,9	2,3	1,21
	m	±0,1[1]	±0,1	±0,1[1]	±0,2 [1]	±0,13
IgA (g/l)	M	1,2	1,1	1,9	2,1	1,34
	m	±0,1	±0,1	±0,1	±0,2	±0,07
IgE (IU)	M	52,1	49,3	178,3	108,7	60,23
	m	±5,3	±3,4	±22,3[1,2]	±16,0[1,2]	±7,4
IgG(g/l)	M	11,5	12,8	11,9	13,0	10,5
	m	±0,9	±1,6	±1,0	±1,9	±1,1
Blasttransformation reaction with FGA (%)	M	81,3	82,1	69,1	76,0	82,2
	m	±1,9	±2,1	±2,0[1,2]	±1,8	±2,5

Table 2 continuation.

Parameters		First group (minor disease severity) (n=56)		Second group (mild disease severity) (n=54)		Control group (n=22)
		Acute phase	Early con valescence phase	Acute phase	Early con valescence phase	
Circulating immune complexes	M	112,3	108,6	148,2	118,8	105,2
	m	±10,1	±9,6	±11,7[1,2]	±7,2	±8,1
IL-4 (pg/ml)	M	72,1	68,2	154,1	114,4	21,1
	m	±4,6[1]	±4,1[1]	±13,1[1,2]	±10,9[1,2]	±1,9
TNF-α (pg/ml)	M	78,1	66,3	46,1	41,9	35,8
	m	±4,8[1]	±3,8[1]	±4,0[1,2]	±3,2[2]	±3,3
IFN-γ (pg/ml)	M	40,1	37,9	27,1	38,7	28,2
	m	±2,3[1]	±2,1[1]	±2,1	±2,1[1]	±2,3
IL-4/IFN-γ	M	1,8	1,8	4,9	2,9	0,8
	m	±0,3[1]	±0,3[1]	±0,3[1,2]	±0,3[1,2]	±0,1

Notes:

1. Data differ reliably (p<0,05) from control group

2. Data differ reliably (p<0,05) from group with minor disease severity

Therefore, the increase in immunoglobulin production along with low content of cytotoxic lymphocytes point to the humoral – mediated orientation of the immune response in acute phase of mild disease severity

Blood cytokine levels are also represented in table 2.

In IM patients with minor disease severity in both developmental stages the increased levels of TNF-α prevailed. TNF-α is a cytokine that is associated with cellular type of immune response.

In IM patients with minor disease severity in both developmental stages the increased levels of TNF-α prevailed. TNF-α is a cytokine that is associated with cellular type of immune response. In the same time, in patients with mild disease severity IL-4, the main cytokine of T helper (Th_2) II type cells, dominated. It should be noted that significant differences in values of IFN -γ levels in different disease severity: in minor disease severity this parameter in both IM stages was higher than that of the control, and in mild disease severity in acute stage did not vary from control values, ands gradually increased in early reconvalescence period. It allows us to assume that in case of expressive immune defence reactions of the organisms (antivirus interferon activation) for intracellular virus reproduction the severity of IM is relatively minor.

One of the manifestations of T cell disbalance in IM patients is the damage of the ratio of Il-4 and IFN- γ production by corresponding T cell types (T_2 and T_1), in which the first has antinflammatory and the second - proinflammatory effect [7, 14].

In minor IM disease severity in acute phase this ratio was higher than the control level more than in 2, 4 times and hasn't undergone any significant changes in early reconvalescence period.

The obtained data show that there is a dependence of the blood cytokine concentration levels from disease severity.

IM disease of mild severity was characterized by an increase of this parameter in 7 times compared to the control. In disease dynamics the decrease of this parameter in the group was very slow, and in early reconvalescence period the IL-4/IFN-γ ratio was 4 times higher than the control level.

CONCLUSION

1. There is a direct dependence between the severity of IM disease and changes in leukogram and immunogram. Sufficient levels of lymphocytes with cytotoxic properties - CD_8 and natural killer cells CD_{16}, satisfactory response of T-lymphocytes in RBTL with FGA reaction, unchanged level of CD_{19}, increased concentration values of TNF -α, IFN-γ, relatively low synthesis levels of IgA, IgE and circulating complexes accumulation point to the predominantly cellular - mediated immune response in patients with minor disease severity of IM.

2. The decrease in quantity of CD_8 and CD_{16} populations, suppression of RBTL with FGA reaction, increase in CD_{19} cells content, IgA and, in particular, IgE synthesis activation, significant increase of circulating immune complexes level and excess of IL-4 content over IFN-γ points to the predominantly humoral-mediated orientation of immune response in mild disease severity of IM.

3. The differences in immune response parameters in minor and mild disease severity of IM, that were studied in present work, point to the need of differentiated approach of immune modulators application in complex of therapeutic measures.

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УДК 616.988.55-058.8-07.

КЛІНІКО-ІММУНОЛОГІЧНІ АСПЕКТИ ПЕРЕБІГУ ГОСТРОГО ІНФЕКЦІЙНОГО МОНОНУКЛЕОЗУ

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Був досліджений зв`язок між тяжкістю клінічних проявів и особливостями імунної відповіді у пацієнтів, хворих на гострий інфекційний мононуклеоз (ІМ). Було встановлено, що при легкому ступеню тяжкості перебігу захворювання домінує клітинно-опосередкована спрямованість імунної відповіді. При середньому ступеню тяжкості захворювання на ІМ переважно домінує гуморально-опосередкована спрямованість імунної відповіді. Встановлені дані вказують на необхідність диференційованого підходу при застосуванні імуномодуляторів в ході лікування ІМ при різних ступенях тяжкості захворювання.

Ключові слова: інфекційний мононуклеоз, імунний статус, імунна відповідь

УДК 616.988.55-058.8-07.

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ АСПЕКТЫ ТЕЧЕНИЯ ОСТРОГО ИНФЕКЦИОННОГО МОНОНУКЛЕОЗА

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Была изучена связь между тяжестью клинических проявлений и особенностями иммунного ответа у пациентов, больных острым инфекционным мононуклеозом (ИМ). Было установлено, что при легкой степени тяжести заболевания доминирует клеточно-опосредованная направленность иммунного ответа. При средней степени тяжести ИМ доминирует преимущественно гуморально-опосредованная направленность иммунного ответа. Установленные данные указывают на необходимость дифференцированного подхода при применении иммуномодуляторов в терапии ИМ в зависимости от степени тяжести течения заболевания.

Ключевые слова: инфекционный мононуклеоз, иммунный статус, иммунный ответ.

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The connection between the severity of clinical manifestations and immune response features in patients with acute infectious mononucleosis (IM) was studied. It was established, that in IM patients with minor disease severity dominated the cellular-mediated response. In IM patients with mild disease severity the humoral-oriented immune response predominated. The described above findings suggest the need of differential approach of immune modulators application in IM therapy, depending on the level of disease severity.

Key words: infectious mononucleosis, immune status, immune response.