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Clinical and immunological differences of infectious mononucleosis in children with acute and prolonged course of the disease

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The basis for conducting the study was the absence in the scientific literature of works devoted to the study of clinical and immunological differences of infectious mononucleosis (IM) in children with an acute and protracted course of the disease.

The aim – to determine the clinical and immunological differences of IM in children with acute and prolonged courses in order to improve therapy and rehabilitation of patients.

Materials and methods. A total of 102 children were under clinical and laboratory-instrumental supervision, of which 65 children (group 1) had acute IM, and 37 (group 2) had a prolonged course.

Results. The severity of lymphoproliferative and hepatosplenic syndromes at the onset of IM can be used as one of the criteria for the probable development of a prolonged course of the disease. The formation of a protracted course is accompanied by a decrease in the content of CD3 less than 50%; CD4 less than 31% and CD8 less than 15%, as well as an increase in the levels of interleukin 1 (IL1) over 20.0 pg/ml (3.5 times more often compared to the group 1), tumor necrosis factor α (TNFα) up to 20.0 pg/ml (1.9 times more often) and a very high level of interleukin 4 (IL4) – over 30.1 pg/ml. Patients of the group 2 were characterized by increased CD22 levels, low levels of immunoglobulins (Ig) IgA, IgM (less than 1.1 g/l), and IgG (less than 10.0 g/l).

Conclusions. Indicators of cellular and humoral immunity influence the course of IM. The formation of the acute course of IM in children is accompanied by activation of both cellular and humoral immunity at the onset of the disease. The prolonged course of IM is characterized by depression of the T-cell link of immunity, as well as inhibition of antibody genesis. The prolonged course of the disease is formed against the background of weak activation of pro-inflammatory interleukins (IL1, TNFα) and significant – anti-inflammatory IL4.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution mentioned in the paper. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: children, infectious mononucleosis, immunity.

Клініко-імунологічні відмінності інфекційного мононуклеозу в дітей із гострим і затяжним перебігом хвороби

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Підґрунтям для проведення дослідження стала відсутність у науковій літературі робіт, присвячених вивченню клініко-імунологічних відмінностей інфекційного мононуклеозу в дітей із гострим і затяжним перебігом хвороби

Мета – визначити клініко-імунологічні відмінності ІМ у дітей із гострим та затяжним його перебігом задля удосконалення терапії та реабілітації хворих.

Матеріали та методи. Під клінічним та лабораторно-інструментальним наглядом перебувало 102 дитини, з яких у 65 дітей (1 група) ІМ мав гострий перебіг, у 37 (2 група) – затяжний.

Результати. Виразність лімфопроліферативного та гепатолієнального синдромів у дебюті ІМ можна використовувати як один із критеріїв ймовірного розвитку затяжного перебігу хвороби. Формування затяжного перебігу супроводжується зниженням вмісту CD3 менше ніж 50%; CD4 менше ніж 31% і CD8 менше ніж 15%, а також підвищенням рівнів інтерлейкіна 1 (ІЛ1) понад 20,0 пг/мл (у 3,5 раза частіше порівняно з 1 групою), фактору некрозу пухлин α (ФНП α) до 20,0 пг/мл (у 1,9 раза частіше) і дуже високим рівнем ІЛ4 – понад 30,1 пг/мл. Для пацієнтів групи 2 характерними були підвищення вмісту CD22, низькі рівні імуноглобулінів (Ig) IgA, IgM (менше ніж 1,1 г/л) і IgG (менше ніж 10,0 г/л).

Висновки. Показники клітинної та гуморальної ланок імунітету впливають на варіант перебігу ІМ. Формування гострого перебігу ІМ у дітей супроводжується активацією як клітинної, так і гуморальної ланок імунітету в дебюті захворювання. Для затяжного перебігу ІМ притаманна депресія Т-клітинної ланки імунітету, а також гальмування антитілогенезу. Затяжний перебіг хвороби формується на фоні слабої активації прозапальних інтерлейкінів (ІЛ1, ФНПα) та значної – протизапального ІЛ4.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження схвалено місцевим етичним комітетом зазначеної в роботі установи. На проведення дослідження отримано інформовану згоду батьків.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діти, інфекційний мононуклеоз, імунітет.

One of the most common childhood diseases is infectious mononucleosis (IM) [21]. According to World Health Organization (WHO) statistics (2018), in various countries of the world, Epstein-Barr virus (EBV) infects from 60% to 98% of the population, while only 20–30% of people have a manifest (active) form of the infectious process in the form of a disease [16,25]. The results of the research of the last decade force us to reconsider the attitude towards this disease as completely benign and prove the possibility of its unfavorable course with the formation, in some cases, of pathological changes that threaten the life of the patient [19,20].

In the available literature, the issue of etiology, clinical and laboratory diagnosis of IM in children is sufficiently thoroughly covered [6]. Many works are devoted to the important role of immunity in IM course formation [4,14]. It is known that the clinical manifestations of any disease, including IM, are determined in many cases by factors of the immune response, which include the cellular and humoral links of immunity [12]. The latter are able to excessively increase inflammatory effects and contribute to the fading of disease clinical manifestations, or, on the contrary, lead to an unfavorable course of the disease: its chronicity, and often – the formation of pathological changes that threaten human life [2,15]. However, despite intensive studies of the clinical and immunological characteristics of IM, there is no unequivocal opinion regarding the criteria for the course of this pathology [7,13,23].

The ***aim*** of the work is the determination of clinical and immunological differences in infectious mononucleosis in children with acute and prolonged courses.

Materials and methods of the study

102 children aged three to fifteen with IM were under supervision. 76 (74.5%) patients had a moderately severe form of the disease, 26 (25.5%) had a severe form. The severity of the disease was established on the basis of disease clinical manifestations and the degree of changes in laboratory analyses and instrumental data.

All children underwent a standard clinical and laboratory-instrumental examination. The diagnosis of IM was verified by Polymerase Chain Reaction (PCR) (detection of Epstein–Barr virus (EBV) deoxyribonucleic acid (DNA) in blood) and Enzyme-Linked Immunosorbent Assay (ELISA) (anti-EBV immunoglobulin (Ig) M and IgG. To study the course of IM observation was carried out, which made it possible to diagnose an acute IM in 65 (63.7%) children (the Group 1), and a prolonged one in 37 (36.7%) (the Group 2). All children received therapy according to the approved protocols (Order of the Ministry of Health of Ukraine No. 354 dated 07/09/2004). The control group consisted of 28 healthy children, similar in age and gender.

Criteria for including children in the study: 1) age from three to fifteen years; 2) clinically and laboratory confirmed diagnosis of Epstein–Barr virus etiology Infectious Mononucleosis (ELISA, PCR); 3) informed consent of patients (their parents) to the study.

Criteria for excluding patients from the study: 1) age up to three and over fifteen years; 2) the presence of severe background pathology (autoimmune diseases, chronic diseases in the acute stage, oncohematological pathology, etc.); 3) other viral infections, including herpesviruses – human herpesvirus (HHV) 1, 2, 6, 7 types, cytomegalovirus (CMV), which were ruled out by PCR and ELISA methods.

The study of the state of the cellular link of the immune response was carried out by the method of monoclonal antibodies (a set of reagents of the Scientific and production laboratory «Granum» (Ukraine), for which heparinized blood of patients was used. Interleukin levels (IL1β, IL4, TNFα) in blood serum were determined by the solid-phase immunoenzymatic method using standard sets of reagents (a set of reagents «Human IL-Platinum ELISA» of the company «Novamedline» (Germany) according to the instructions. The state of the humoral link of the immune response (the content of IgM, IgA, and IgG in the blood serum of patients) was determined by the immunoturbidimetric method, using a set of reagents «Biosystems» (Spain).

When processing the research results, the average arithmetic value of the series (M), the mean square deviation (σ), and the error of the average arithmetic value of the series (m) were calculated. The probability of differences between the average values was determined using Student's test (t), Pearson's Chi-squared test, and the relationship between the obtained parameters was evaluated based on the correlation coefficient (r) and the probability of error (p). Statistical processing of the obtained data was carried out using the IBM SPSS 25.0® for

Windows® (Trial version) application program package.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution mentioned in the paper. The informed consent of the patient was obtained for conducting the studies.

The results of the study

The children of both groups were comparable in terms of gender, age, disease severity, and other parameters. The analysis of clinical indicators of IM in patients of the comparison groups revealed differences in individual symptoms at the disease onset (Table 1).

Significant differences between patients in the observation groups were established regarding the frequency and severity of lymphoproliferative syndrome. For example, the size of submandibular lymph nodes greater than 2.1 cm was characteristic of patients in the Group 2 and was determined in 54.1% of patients. This sign occurred 3.2 times less often in patients of the Group 1 – only in 16.9% of children ($p<0.05$). An increase in cervical lymph nodes over 1.1 cm was observed 4.8 times more often in children of the Group 2 (10.8% and 51.4%, respectively, $p<0.05$). The sizes of inguinal and axillary lymph nodes over 0.6 cm were recorded significantly more often also in children of the Group 2 (3.1% and 48.6%, respectively) ($p<0.05$).

An important symptom was the determination of the size of the liver less than 2.5 cm from the edge of the rib, which was diagnosed in 23% of the Group 1 patients, in contrast to 8.1% of cases in the Group 2 ($p<0.05$). Palpation and ultrasound determination of the edge of the liver over 2.6 cm was typical for patients of the Group 2 (91.9% of cases, $p<0.05$). In addition,

Table 1

Frequency of occurrence of clinical symptoms in patients with Infectious Mononucleosis with different course

Indicators	Gradations of indicators	Group 1 (n=65)		Group 2 (n=37)		p
		abs.	%	abs.	%	
Body temperature, C°	<38	19	29.2	15	40.5	>0.05
	≥38	46	70.8	22	59.5	>0.05
Severity of the disease	moderate severity	63	96.9	35	94.6	>0.05
	severe form	2	3.1	2	5.4	>0.05
Sore throat	yes	41	63.0	25	67.5	>0.05
	no	24	37.0	12	32.5	>0.05
Facial swelling	yes	7	10.7	5	13.5	>0.05
	no	58	89.3	32	86.5	>0.05
Pale skin	yes	22	33.8	16	43.2	>0.05
	no	43	66.2	21	56.8	>0.05
Difficulty in nasal breathing	yes	38	58.4	22	59.4	>0.05
	no	27	41.6	15	40.6	>0.05
Tonsillitis	catarrhal	4	6.1	2	5.4	>0.05
	follicular or lacunar	61	93.9	35	94.6	>0.05
Submandibular lymph nodes Sizes, cm	≤2	54	83.1	17	45.9	<0.05
	≥2.1	11	16.9	20	54.1	<0.05
Cervical lymph nodes sizes, cm	≤1.0	58	89.2	18	48.6	<0.05
	≥1.1	7	10.8	19	51.4	<0.05
Inguinal and axillary lymph nodes sizes, cm	≤0.5	63	96.9	19	51.4	<0.05
	≥0.6	2	3.1	18	48.6	<0.01
Enlargement of mesenteric lymph nodes, cm	≤0.5	61	93.9	31	83.7	>0.05
	≥0.6	4	6.1	6	16.3	>0.05
The edge of the liver below the hypochondrium, cm	≤2.5	15	23.0	3	8.1	<0.05
	≥2.6	50	77.0	34	91.9	<0.05
The edge of the spleen below the hypochondrium, cm	≤1.0	46	70.7	18	48.6	<0.05
	≥1.1	19	29.3	19	51.4	<0.05

an increase in the size of the spleen over 1.1 cm was observed 1.7 times more often in the Group 2 (p<0.5). We did not establish significant differences between the groups regarding the frequency of registration of such symptoms as a temperature reaction, sore throat, facial swelling, pale skin, difficulty in nasal breathing, and the nature of tonsillitis (p>0.05).

A difference in the immune response of patients with different courses of IM was revealed. For indicators of the T-system of immunity in patients of the Group 2, a decrease in the content of CD3 by less than 50% was characteristic (in 26.2% and 51.3% of patients, respectively; p<0.05); CD4 – less than 31% (in 32.4% and 62.1%, respectively; p<0.05) and CD8 – less than 15% (in 10.8% and 37.8%, respectively; p<0.01) (Table. 2).

It was determined that in patients of the Group 2, depression of the T-cell link of immunity was significantly more common (p<0.05–0.01) at the onset of the disease. The cytokine profile study revealed that in patients of the Group 2, in comparison with the Group 1, the level of IL1 was less than 20 pg/ml 3.5 times more often (18.5% and 64.8%, respectively; p<0.001); TNFα less than 20.0 pg/ml 1.9 times more often (24.6% and 48.6%, respectively; p<0.05) and a very high level of IL4 – more than 30.1 pg/ml in 2 times more often (20.0% and 40.5%, respectively; p<0.05).

As for the B-system of immunity, in patients of the Group 2, an increased content of CD22 of more than 31% was determined significantly more often (46.2% and 73.0% of patients, respectively; p<0.05). The reaction of the humoral link of the patients was different, which was characterized by a higher frequency of detection of significant changes in the patients of the Group 2 – a low level of IgA less than 1.0 g/l (32.3% and 54.1%, respectively; p<0.05), the level IgM less than 1.1 g/l (24.6% and 62.1%,

Table 2

Immune indicators of children of the compared groups

Indicators	Gradations of indicators	Group 1 (n=65)		Group 2 (n=37)		p
		abs.	%	abs.	%	
CD3, %	≤50	17	26.2	19	51.3	<0.05
	51–60	17	26.2	11	29.8	>0.05
	≥61	31	47.6	7	18.9	<0.05
CD4, %	≤31	21	32.4	23	62.1	<0.05
	≥32	44	67.6	42	37.9	<0.05
CD8, %	≤15	7	10.8	14	37.8	<0.01
	16–30	32	49.2	19	51.4	>0.05
	≥31	26	40,0	4	10.8	<0.01
CD22, %	≤30	35	53.8	10	27.0	<0.05
	≥31	30	46.2	27	73.0	<0.05
IL-1, pg/ml	≤20	12	18.5	24	64.8	<0.001
	20.1–30	10	15.4	6	16.2	>0.05
	≥30.1	43	66.1	7	19.0	<0.001
IL-4, pg/ml	≤30	52	80.0	22	59.5	<0.05
	≥30.1	13	20.0	15	40.5	<0.05
TNFα, pg/ml	≤20	16	24.6	18	48.6	<0.05
	20.1–30	14	21.5	7	18.9	>0.05
	≥30.1	35	53.9	12	32.5	<0.05
Ig A, g/l	≤1.0	21	32.3	20	54.1	<0.05
	≥1.1	44	67.7	17	45.9	<0.05
Ig M, g/l	≤1.0	16	24.6	23	62.1	<0.001
	≥1.1	49	75.4	14	37.9	<0.001
Ig G, g/l	≤10.0	16	24.6	28	75.6	<0.001
	≥10.1	49	75.4	9	24.4	<0.001

respectively; p<0.001) and the level of IgG less 10.0 g / l (respectively in 24.6% and 75.6%; p<0.001).

Discussion

According to the obtained data, at the current stage, both with acute and prolonged IM in children, the symptoms characteristic of the disease are preserved at the debut. The manifestation of the disease began with moderately pronounced intoxication, which was characterized by such symptoms as weakness, decreased appetite, headache, and fever. The data of O.A. Dralova and O.V. Usachova testify to the registration of these symptoms in all IM patients at the onset of the disease [5].

Acute tonsillitis was registered in 100% of cases; its follicular and/or lacunar form was noted in the majority (94.1%) of patients, which coincides with the results of studies [20,26].

Polylymphadenopathy was observed in 100% of cases. At the same time, the size of the submandibular lymph nodes over 2.1 cm (16.9% vs. 54.1%, respectively), the increase in cervical lymph nodes over 1.1 cm (10.8% vs. 51.4%, respectively), as well as the size of the inguinal and axillary lymph nodes over 0.6 cm (48.6% vs. 3.1%, respectively) were characteristic of patients with prolonged IM. Other authors also identified such signs [8,12].

Hepatosplenomegaly was recorded in most cases. An increase in the size of the liver more than 2.5 cm below the hypochondrium was characteristic of patients with a prolonged course (respectively, 77% vs. 91.9%, p<0.05). In the same group, an increase in the size of the spleen over 1.1 cm was more often diagnosed (respectively, 29.3% vs. 51.4%, p<0.05). Our data do not contradict the results of scientists who studied the clinical aspects of various variants of IM in children [9,22].

Complaints about pain in the throat were observed in 63% of cases with an acute IM, and in 67.5% – prolonged. Adenoiditis, the manifestation of which was difficulty in nasal breathing, occurred in 58.4% of the first group patients, in 59.4% – the second group. Swelling of the face (respectively, 10.7% vs. 13.5%) and pallor of the skin (respectively, 33.8% vs. 43.2%) in patients was noted. We found no significant difference in these clinical symptoms in the observation groups (p>0.05). The above-mentioned data coincide with the studies of other authors [5,9].

The acute period of IM in patients with a prolonged course is more often accompanied by depression of the T-cell link of immunity than in patients with an acute course of IM. These data coincide with the data of M. Hayashida (2017), M.M. Popov, and T.I. Liadova (2022) [10,18]. Also, O. Guz, and S. Kuznetsov indicate that a low number of CD8+-lymphocytes in infectious diseases in the patient registers a sluggish, protracted course of the disease with a long period of convalescence and complications [8]; the probability of the accumulation of other viral, bacterial, or fungal diseases increases.

The course of IM depends on the type of activation of T-helper clones. Thus, according to our data, the acute course of IM is formed against the background of hyperproduction of pro-inflammatory IL1, TNFα, and anti-inflammatory IL4 cytokines, which reflects the activation of both T1 and T2-helper responses. Weak activation of pro-inflammatory interleukins (IL1, TNFα) against the background of a significant response of anti-inflammatory IL 4 leads to the formation of a protracted course of IM. This corresponds to an immune response of the T2-helper pathway. Such a ratio of cytokines may indicate the switching of activated T-lymphocytes from Th1-cells, which control the development of cell-mediated mechanisms of immune protection, to Th2-helpers, which determine the formation of antibodies and reactions of immediate Ig E-dependent allergy. In the literature, there are conflicting opinions regarding this conclusion. Most researchers indicate the unidirectionality of changes in the systemic cytokine response during a favorable course of IM: hyperproduction of pro-inflammatory cytokines against the background of a lack of anti-inflammatory ones, which ensures the formation of a Th1-type immune response [11]. However, other authors believe that the lack of protective factors of the humoral link of immunity in the acute phase of infection is the reason for the development of complications and/or the duration of the infectious process [17]. Our results confirm the study of J. Chen et al. (2021) who believe that the transformation of the immune response on the Th2-dependent pathway leads to a violation of the elimination of EBV, with the subsequent development of an unfavorable course and outcomes of the disease [1].

In patients with a protracted course compared to acute IM, an increased content of CD22, as

well as low levels of IgA, IgM less than 1.1 g/l, and IgG less than 10.0 g/l, were more often determined. Similar data were obtained by other scientists [3]. Therefore, the protracted course of IM is formed against the background of increased content of CD22 and a decrease in antibodyogenesis. In our opinion, this paradoxical situation is explained by the reduction of CD4, the role of which is to transform B-lymphocytes (CD22) into plasma cells that produce antibodies. Our assumption does not coincide with the studies of individual authors [24] and requires further study.

Thus, the clinical picture of IM, the response of the cellular and humoral links of immunity in sick children already in the early stages of the manifestation of the disease, reflects a possible variant of its further course, and these signs can be used as prognostic criteria.

Conclusions

1. Among the clinical manifestations of IM at the stage of its manifestation, a prognostic sign of the possible further formation of a protracted course may be the presence and severity of lymphoproliferative and hepatolienal syndromes.

2. The acute course of IM in children is accompanied by the activation of both cellular and humoral links of immunity, which is manifested in the form of an increase in the relative content of CD3+, CD4+, CD8+, and CD22+ and the levels of immunoglobulins M and A. The protracted course of IM at the onset of the disease is characterized by depression of the T-cell link of immunity in the form of a decrease in the relative content of CD3+, CD4+, and CD8+ lymphocytes and an increase in CD22+, as well as inhibition of antibody formation.

3. At the onset of acute IM, activation of the T1 and T2 helper response is noted, which manifests itself in the form of a significant increase in IL1, TNFα, and moderate – IL4. The prolonged course of IM is formed against the background of an imbalance of pro- and anti-inflammatory cytokines, which consists in the relative dominance of the anti-inflammatory cytokine IL4 over pro-inflammatory ones IL1 and TNFα.

Prospects for further research. Considering the urgency of the problem of infectious mononucleosis in pediatric practice, further studies of clinical and immunological differences in the course are extremely relevant from the point of view of a deeper understanding of the mechanisms of the development of the disease and prediction of the unfavorable course of the pathology.

The authors declare no conflict of interest.

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