**UDC: 616.98:578.825.13-053.2:616.211/.22-08.85**

**THE VALUE OF THE MICROBIAL FLORA OF THE NASAL AND OROPHARYNGEAL MUCOSA IN THE FORMATION OF CLINICAL AND IMMUNOLOGICAL FEATURES OF INFECTIOUS MONONUCLEOSIS IN CHILDREN**

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**Abstract**

**Objective.**The article presents the results of studies to determine the significance of the microbial flora of the nasal mucosa and oropharynx in the formation of the clinical course and immune response in children with infectious mononucleosis (IM).

**Materials and methods.** Under the supervision were 93 children aged three to nine years, patients with mononucleosis. In 32 children (first group), Streptococcus pyogenes at concentrations of 10-5 and higher was isolated during bacteriological examination of the mucosa of the nasopharynx and oropharynx. 30 (second group) - 10-4 degrees or less. In 31 (the third group), Staphylococcus aureus, Spirochetae buccalis, E. Coli and other bacteria, except streptococcus, were sown in smears from the mucous membrane of the nasoropharynx. The immune status of patients was assessed by indicators of levels of lymphocytes CD3+, CD4+, CD8+, CD22+ and the content of interleukins 1β, 4, TNFα. **Results.** The acute period of the mononucleosis in children of the first group was characterized more severe symptoms of intoxication, more severe morphological changes in the tissues of the tonsils, lymph nodes, liver and spleen. Also a significant decrease in the relative amount of CD3+, CD4+, CD8+ was observed compared with the indicators of children of the second and third groups. The increase in blood CD22+ content was more significant in children of the first group. The content of pro-inflammatory IL-1β and TNF-α in patients of all groups was significantly higher than in healthy children. The IL-4 increased in children of the second and third groups. In the period of early convalescence in children of the second and third groups, the relative content of CD3+, CD4+, CD8+ cells approached the corresponding indices of the control group. This was not observed in children of the first group. CD22+ levels in all observation groups decreased by the convalescence period, but remained high compared with the control group. In children of the studied groups, by the period of reconvalescence, a decrease in the levels of IL-1β, TNF-α is noted, more significant in children of the second and third groups. At the same time, in children of the first group, the level of pro-inflammatory interleukins by the period of reconvalescence remained at high numbers. The content of IL-4 was a significant difference in the indicators of its content in comparison with the digital characteristics of healthy ones in children of the second and third groups. **Conclusion.** An analysis of the results of the study found that the presence of streptococcus in its high concentration on the mucosa of the nosopharynx of children with mononucleosis already contributes to the formation of cellular immunosuppression and a pronounced reaction of pro-inflammatory interleukins at the initial stage of the disease, which, in general, leads to aggravation of the clinical manifestations of the disease and, in our opinion, may be a causative factor of a possible unfavorable course of the disease.

*KEYWORDS:* Children, infectious mononucleosis, Epstein-Barr virus, microbial flora, immunity.

**ЗНАЧЕНИЕ МИКРОБНОЙ ФЛОРЫ СЛИЗИСТОЙ ОБОЛОЧКИ НОСО - И РОТОГЛОТКИ В ФОРМИРОВАНИИ КЛИНИКО-ИММУНОЛОГИЧЕСКИХ ОСОБЕННОСТЕЙ ИНФЕКЦИОННОГО МОНОНУКЛЕОЗА У ДЕТЕЙ**

**Гузь Е.В., Кузнецов С.В.**

**Цель.** В статье представлены результаты исследований по определению значимости микробной флоры слизистой оболочки носа и ротоглотки в формировании клинического течения и иммунного ответа у детей с инфекционным мононуклеозом (ИМ).

**Материалы и методы.** Под наблюдением находились 93 ребенка болеющие мононуклеозом в возрасте от трех до девяти лет. У 32 детей (первая группа) Streptococcus pyogenes был выделен при бактериологическом исследовании слизистой оболочки носоглотки и ротоглотки в концентрациях 10-5  и выше. 30 (вторая группа) - 10-4 или меньше. У 31 (третья группа) Staphylococcus aureus, Spirochetae buccalis, E. Coli и другие бактерии, кроме стрептококка, были посеяны в мазках из слизистой оболочки носоглотки. Иммунный статус пациентов оценивали по показателям уровня лимфоцитов CD3 +, CD4 +, CD8 +, CD22 + и содержанию интерлейкинов 1β, 4, ФНО-α.

**Результаты.** Острый период мононуклеоза у детей первой группы характеризовался более выраженными симптомами интоксикации и более выраженными морфологическими изменениями в тканях миндалин, лимфатических узлов, печени и селезенки. Также наблюдалось значительное снижение относительного количества CD3 +, CD4 +, CD8 + по сравнению с показателями детей второй и третьей групп. Увеличение содержания CD22 + в крови было более значительным у детей первой группы. Содержание провоспалительных ИЛ-1β и ФНО-α у пациентов всех групп было значительно выше, чем у здоровых детей. ИЛ-4 повышен у детей второй и третьей групп. В период раннего выздоровления у детей второй и третьей групп относительное содержание клеток CD3 +, CD4 +, CD8 + приблизилось к соответствующим показателям контрольной группы. Этого не наблюдалось у детей первой группы. Уровни CD22 + во всех группах наблюдения снижались к периоду выздоровления, но оставались высокими по сравнению с контрольной группой. У детей исследуемых групп к периоду реконвалесценции отмечается снижение уровней ИЛ-1β, ФНО-α, более значимое у детей второй и третьей групп. В то же время у детей первой группы уровень провоспалительных интерлейкинов к периоду реконвалесценции оставался высоким. Содержание ИЛ-4 достоверно отличалось по показателям его содержания по сравнению с цифровыми характеристиками здоровых у детей второй и третьей групп.

**Выводы.** Анализ результатов исследования показал, что наличие стрептококка в его высокой концентрации на слизистой оболочке носоглотки у детей с мононуклеозом способствует формированию клеточной иммуносупрессии и выраженной реакции провоспалительных интерлейкинов на начальной стадии заболевание, которое, в общем, приводит к обострению клинических проявлений заболевания и, по нашему мнению, может быть причиной возможного неблагоприятного течения заболевания.

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ЗНАЧЕННЯ МІКРОБНОЇ ФЛОРИ СЛИЗОВОЇ ОБОЛОНКИ НОСО - І РОТОГЛОТКИ У ФОРМУВАННІ КЛІНІКО- ІМУНОЛОГІЧНИХ ОСОБЛИВОСТЕЙ ІНФЕКЦІЙНОГО МОНОНУКЛЕОЗУ У ДІТЕЙ

**Гузь О.В., Кузнєцов С.В.**

**Мета.** У статті представлені результати досліджень по визначенню значущості мікробної флори слизової оболонки носо- і ротоглотки у формуванні клінічного перебігу та імунної відповіді у дітей з інфекційний мононуклеоз (ІМ).

**Матеріали та методи.** Під спостереженням знаходилися 93 дитини хворі на мононуклеоз у віці від трьох до дев'яти років. У 32 дітей (перша група) Streptococcus pyogenes був виділений при бактеріологічному дослідженні слизової оболонки носоглотки і ротоглотки в концентраціях 10-5 і вище. 30 (друга група) - 10-4 або менше. У 31 (третя група) Staphylococcus aureus, Spirochetae buccalis, E. Coli і інші бактерії, крім стрептокока, були посіяні в мазках зі слизової оболонки носоглотки. Імунний статус пацієнтів оцінювали за показниками рівня лімфоцитів CD3 +, CD4 +, CD8 +, CD22 + і змістом интерлейкинов 1β, 4, ФНП-α.

**Результати.** Гострий період мононуклеозу у дітей першої групи характеризувався більш вираженими симптомами інтоксикації і більш вираженими морфологічними змінами в тканинах мигдалин, лімфатичних вузлів, печінки і селезінки. Також спостерігалося значне зниження відносної кількості CD3 +, CD4 +, CD8 + в порівнянні з показниками дітей другої і третьої груп. Збільшення вмісту CD22 + в крові було більш значним у дітей першої групи. Зміст прозапальних ІЛ-1β і ФНП-α у пацієнтів всіх груп було значно вище, ніж у здорових дітей. ІЛ-4 підвищений у дітей другої і третьої груп. У період раннього одужання у дітей другої і третьої груп відносний вміст клітин CD3 +, CD4 +, CD8 + наблизилося до відповідних показників контрольної групи. Цього не спостерігалося у дітей першої групи. Рівні CD22 + у всіх групах спостереження знижувалися до періоду одужання, але залишалися високими в порівнянні з контрольною групою. У дітей досліджуваних груп до періоду реконвалесценції відмічається зниження рівнів ІЛ-1β, ФНП-α, більш значуще у дітей другої і третьої груп. У той же час у дітей першої групи рівень прозапальних інтерлейкінів до періоду реконвалесценції залишався високим. Зміст ІЛ-4 достовірно відрізнялося за показниками його змісту в порівнянні з цифровими характеристиками здорових у дітей другої і третьої груп.

**Висновки.** Аналіз результатів дослідження показав, що наявність стрептокока в його високій концентрації на слизовій оболонці носоглотки у дітей з мононуклеозом сприяє формуванню клітинної імуносупресії і вираженої реакції прозапальних інтерлейкінів на початковій стадії захворювання, яке, в загальному, призводить до загострення клінічних проявів захворювання і, на нашу думку, може бути причиною можливого несприятливого перебігу захворювання.

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**INTRODUCTION**

Diseases of herpes virus etiology, including infectious mononucleosis (IM), of which Epstein-Barr virus (EBV) (herpes type 4 virus) is a causative factor, are currently a widespread pathology among the child population, both in Ukraine and abroad [1]. According to WHO statistics, more than 5 million children die every year from these diseases and their consequences in the world [2].

The results of laboratory studies of recent years convincingly prove infection with the Epstein-Barr virus in almost 98% of people living on planet Earth [3]. However, EBV diseases with the presence of appropriate symptoms are recorded much less frequently [4]. It is believed that in children under the age of 2 years, the disease can occur in the clinical form like acute respiratory viral infections, which is apparently due to their initial contact with the virus and, possibly, a feature of the immune response [5]. At the same time, in older people, with the development of a typical clinical picture of infectious mononucleosis [6].

The clinical picture of IM is characterized by fever, tonsilopharyngitis, lymphadenopathy, hepato- and splenomegaly, specific changes in peripheral blood parameters [7].

Scientists argue that the clinical picture of the disease and the complications that can develop with IM depend on the microbial flora of the nasal and oropharynx mucosa of the patients [8,9]. However, there are very few works devoted to the study of this problem in the literature, and their results are very contradictory [10].

Some authors prove that tonsillitis in IM has a viral and bacterial origin, while the role of the microbial flora is dominant [11,12]. Others indicate the leading role of the virus in the formation of pathological changes in the lymphoid formations of the nose and oropharynx of patients, and the participation of pathogenic microorganisms in the occurrence of tonsillitis is considered secondary [13,14].

The difficulties in establishing the role of certain microorganisms in the defeat of the oropharynx are also due to the fact that healthy people have an extremely diverse microbial flora in the oral cavity and tonsils [15].

Staphylococus epidermidis, Streptococcus pyogenes, Streptococcus pneumoniae and other Streptococcus, Enterococcus, Lactobacillus Actinomices, Neisseria, Actinomyces, Clostridium, Pseudomonas, Staphylococus aureus are most often detected in the oral cavity and nasopharynx. Streptococcus dominates of all these bacteria and makes up 30-60% of the entire microflora. [16].

Thanks to recent studies, it was found that in 60-80% of healthy children with mucous membranes of the nasopharynx and oropharynx, Streptococcus is sown, which has a high pathogenic potential and can cause the development of a disease [17].

However, many scientists claim that the presence of Streptococcus is not in all concentrations pathogenic [18].

It is known that the clinical picture and outcome of any disease depends on the timeliness and adequacy of the immune responses of the human body. This is especially observed with herpesvirus pathology, including mononucleosis, a disease that is considered as a disease of the immune system [19]. Active proliferation of EBV in all lymphoproliferative organs leads to their structural changes, which is reflected in the immune response (cellular and humoral) [20].

At the same time, in the available literature there are practically no works that would consider the effect of the microbial flora of the nasopharynx on the formation of the immune response of patients, and hence the clinical picture of the disease, its course and outcomes. In our opinion, studies in this direction will improve the prediction of the course of IM in children, outcomes and more reasonably outline ways to increase the effectiveness of treatment of patients.

**OBJECTIVE**

**T**o determine the significance of the microbial flora of the nasal and oropharyngeal mucosa in the formation of the clinical course and immune response of children with infectious mononucleosis.

**MATERIALS AND METHODS**

Under the supervision were 93 children aged three to nine years, patients with mononucleosis of moderate severity who were treated at the Regional Children's Infectious Clinical Hospital in Kharkiv, Ukraine. The diagnosis of IM was verified on the basis of positive results for the search for disease markers by ELISA (anti-EBV IgM and IgG) and PCR (detection of EBV DNA in the blood). In 32 children (first group), Streptococcus pyogenes at concentrations of 10-5 and higher was isolated during bacteriological examination of the mucosa of the nasopharynx and oropharynx. 30 (second group) - 10-4 degrees or less. In 31 (the third group), Staphylococcus aureus, Spirochetae buccalis, E. Coli and other bacteria, except streptococcus, were sown in smears from the mucous membrane of the nasoropharynx. The immune status of patients was assessed by indicators of levels of populations and subpopulations of peripheral blood lymphocytes, which were determined by indirect immunofluorescence using monoclonal antibodies to surface antigens of lymphocytes CD3+, CD4+, CD8+, CD22+. As well as the content in their blood of interleukins 1β, 4, TNFα. The studies were carried out in the acute period (1-2 days of illness) and in the period of early convalescence (8-13 days). As a comparison, we took the corresponding indicators of 30 healthy children of the same age and gender.

Static processing of the results was carried out using computer programs Excel and Statistica 6.0. The reliability of the difference in values was revealed using Student's test and Fisher's method. Differences were considered significant at a significance level of P<0.05.

**RESULTS AND DISCUSSIONS**

Table 1.

Clinical and laboratory characteristics of the acute period of mononucleosis in children of the compared groups

|  |  |
| --- | --- |
| Clinical and laboratory manifestations of the disease |  Сompared groups (М±m) |
| I(n=32) | II (n=30) | IIІ (n=31) |
| 1.Temperature of the body | 39.2±0.21°C 1,2 | 38±0.31°C | 37.7±0.27°C |
| 2. Tonsillitis:catarral (%)purulent (quinsy) (%) | 11.28±1.911,288.72±2.041,2 | 29.56±2.0371.44±1.87 | 33.32±1.4367.67±0.09 |
| 3. Lymph node sizes centimeters (cm)- submandibular- cervical | 2.5±0.131,21.5±0.311,2 | 1.5±0.321.2±0.24 | 1.5±0.120.9±0.32 |
| 4. Enlargement of the spleen (сm) | 3.3±0.26 1,2  | 2.1±0.24  | 2.0±0.13  |
| 5. Enlargement of the liver (сm) | 2.1±0.241,2 | 1.03±0.17 | 1.03±0.36 |
| 6. Analysis of the blood:- count of the neutrophils (%)- count of the lymphocytes (%) | 62.08±1.621,234.03±1.221,2 | 41.33±1.9749.17±2.03 | 42.26±1.1350.13±1.17 |

Note:

Р1– probability of the characteristic of the first group relative to the second group;

Р2 – probability of the characteristic of the first group relative to the third group;

Р3 – probability sign between the second and third groups.

When comparing the clinical and laboratory parameters of the children of the compared groups, it was found that the children, whose Streptococcus pyogenes was isolated on the rhinopharyngeal mucosa at concentrations of 10-5 and higher, the clinical picture was characterized in the onset of the disease by a higher temperature reaction of the body, more severe morphological changes in the tissues of the tonsils, significantly more pronounced increase in submandibular and cervical lymph nodes, liver and spleen. In the blood of children of the first group, higher numbers of the relative content of neutrophils and low lympho-monocytes were determined.

In the children of the first group, the course of the disease was longer and amounted to 17.56 ± 1.56 days, the second –13.24 ± 1.37 and in the children of the third group –10.24 ± 1.54 days.

The differences in the severity of clinical manifestations and the results of paraclinical examination which was given, as well as taking into account the importance of immune factors in this, we conducted studies to determine the immune status of children in all groups.

Table 2.

Indicators of the immune status of patients in the acute period of mononucleosis (M ± m)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Indicator | First group(n=32) | Second group(n=30) | Third group(n=31) | Control group (n=30) |
| CD 3+, % | 47.16±0.741,2,3 | 57.30±0.521 | 58.10±0.721 | 60.60±1.20 |
| CD 4+, % | 30.57±0.421,2,3 | 33.86±0.341 | 34.02±0.221 | 36.30±0.75 |
| CD 8+, % | 19.37±0.341,2,3 | 23.40±0.391 | 23.60±0.121 | 25.70±0.68 |
| CD 22+, % | 35.60±0.251,2,3 | 32.56±0.421 | 32.63±0.281 | 17.30±0.79 |
| Interleukins: pg / mlIL -1β | 18.66±1.191,2,3 | 9.80±0.911 | 7.90±0.841 | 5.32±1.73 |
| IL – 4 | 3.66±0.241,2,3 | 5.40±0.301 | 5.10±0.211 | 2.06±0.94 |
| TNF - α | 11.20±1.431,2,3 | 6.90±1.121 | 6.30±1.081 | 2.69±1.67 |

Note here and further:

Р1 – reliability of the difference in the digital values of indicators of healthy and sick children;

Р2 –probability of the characteristic of the first group relative to the second group;

Р3 – probability of the characteristic of the first group relative to the third group;

Р4 – probability sign between the second and third groups.

It should be noted that in children with a high degree of insemination of streptococcus of the nasal and oropharyngeal mucosa in the acute period of the disease, a significant decrease in the number of СD3+, СD4+ СD8+ was observed compared with the indicators of children of the second and third groups (P2,P3<0.05). The increase in blood CD22+ content was more significant in children of the first group, (P1<0.05, P2<0.05, P3<0.05).

Some authors argue that a violation of the cellular-humoral reactivity of the body with a tendency to suppress cell-mediated mechanisms and enhance the humoral mechanisms of the immune response affects the clinical and biochemical manifestations of the disease and leads to its long-term undulating course. [21].

At the same time, other studieshave revealed an increase in the activity of the cellular component of the immune response in children with IM in the acute period of the disease. In our opinion, the immune response in mononucleosis depends on many factors, including the patient's age, activity of the process, viral load, the initial background of the patient and the presence of comorbidities, etc., and needs further investigation [22].

However, these studies concerned children suffering from mononucleosis in the form of mono-infection without taking into account the presence of coccal flora on the mucous membranes of the nasopharynx and its amount, which may affect the immune response of children.

All children have characteristic signs of activation of anti-infection protection in the acute period of mononucleosis. The content of pro-inflammatory IL-1β in blood serum in the onset of the disease in patients of all groups was significantly higher than in healthy children (P1<0.05). In children with additional infection of the nasal and oropharynx mucosa with streptococcus with a high degree of seeding, the concentration of IL-1β was 18.66 ± 1.19 pg/ml and was significantly higher than the corresponding indicators of the second group - 9.8 ± 0.91 pg/ml (P2<0.05) and the third - 7.90 ± 0.84 pg ml (P3<0.05).

The acute period of mononucleosis is accompanied by a significant increase in the blood level of patients with TNF-α compared with its content in healthy children (P1<0.05), while the level of pro-inflammatory TNF-α in patients of the first group was significantly higher than similar indicators in children of the second and third groups (P2<0.50; P3<0.05).

When studying the levels of IL-4 in the blood serum of children of the studied groups, an increase in its content was revealed in comparison with healthy children, however, a significant difference in its content was determined only in the indicators of children of the second, third and control groups (P2<0.05, P3<0.05). And although in patients of the first group there was an increase in the level of IL-4 in the blood, it was less significant than in children of the second and third groups to healthy children (P1<0.05).

In the period of early convalescence in children of the second and third groups, the relative content of CD3+, CD4+, CD8+ cells approached the corresponding indices of the control group (P2,3≥0.05), which indicated a tendency to normalize the cellular immunity of patients. This was not revealed in children which were seeding streptococcus with a high degree on the mucosa of the nasal and oropharynx. in children of the first group, the content of CD3+, CD4+, CD8+ increased in the period of IM convalescence compared with the acute period, but was significantly lower (P1<0.05) compared with the control group. As in the acute period, in the period of IM convalescence in children of the first group, signs of a cellular immune response deficiency were found, which must be taken into account in the dynamics of correction of the therapy (Table 3).

Table 3.

Indicators of the immune status of patients in the early reconvalescence period of mononucleosis (M ± m)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Indicator | First group(n=32) | Second group(n=30) | Third group(n=31) | Control group (n=30) |
| CD 3+, % | 51.03±0.701,2,3 | 59.83±0.91,4 | 60.46±0.21,4 | 60.60±1.20 |
| CD 4+, % | 31.83±0.381,2,3 | 35.53±0.341 | 35.53±0.121 | 36.30±0.75 |
| CD 8+, % | 21.07±0.461,2,3 | 25.40±0.381 | 25.40±0.041 | 25.70±0.68 |
| CD 22+, % | 33.97±0.351,2,3 | 30.36±0.481,4 | 28.08±0.781,4 | 17.30±0.79 |
| Interleukins: pg / mlIL -1β | 15.03±1.281,2,3 | 8.9±0.941,4 | 8.0±0.541,4 | 5.32±1.73 |
| IL – 4 | 4.60±0.852,3 | 6.30±0.621 | 6.30±0.481 | 2.06±0.94 |
| TNF - α | 7.9±0.421,2,3 | 5.6±0.491 | 5.6±0.291 | 2.69±1.67 |

In the period of early convalescence in children of the second and third groups, the relative content of CD3+, CD4+, CD8+ cells approached the corresponding indices of the control group (P2,3≥0.05), which indicated a tendency to normalize the cellular immunity of patients. This was not revealed in children which were seeding streptococcus with a high degree on the mucosa of the nasal and oropharynx. in children of the first group, the content of CD3+, CD4+, CD8+ increased in the period of IM convalescence compared with the acute period, but was significantly lower (P1<0.05) compared with the control group. As in the acute period, in the period of IM convalescence in children of the first group, signs of a cellular immune response deficiency were found, which must be taken into account in the dynamics of correction of the therapy.

CD22+ levels in all observation groups decreased by the convalescence period, but remained high compared with the control group (P1<0.05).

In children of the studied groups, by the period of reconvalescence, a decrease in the levels of IL-1β, TNF-α is noted, which is more significant in children of the second and third groups, in which there is no mathematical difference in the levels of these interleukins in blood compared with healthy children (P2,3> 0.05).

At the same time, in children of the first group, the level of pro-inflammatory interleukins by the period of reconvalescence remained at high numbers (P1<0.05).

The content of anti-inflammatory interleukin-4 in the blood of children by the period of their recovery exceeded these indicators of the acute period. However, in the reconvalescence period only in children of the second and third groups there was a significant difference in IL-4 in comparison with the digital characteristics of healthy ones (P2,3<0.05).

**CONCLUSIONS**

1. Microorganisms that are present on the mucous membrane of the nasal and oropharynx have a different effect on the formation of the immune response of children with mononucleosis. This explains the differences in the severity of clinical symptoms and the duration of the disease.

2. Streptococcus is the most aggressive microbial structure that negatively affects the immune response of patients with mononucleosis. Moreover, the degree of the indicated effect is proportional to the level of streptococcus contamination of the nasopharyngeal mucosa.

3. The most significant deviations from the norm of the indicators of the immune response of patients with mononucleosis are observed in children in whom streptococcus 10-5 and higher is sown on the mucous membrane of the nasal and oropharynx. In our opinion, the immunosuppressive state is a factor in the prolongation of the disease.

4. The differences that were identified as a result of the study can serve as an additional criterion for predicting the course of mononucleosis and the choice of therapy, which will reduce adverse outcomes and improve treatment.

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