

CYTOKINE PROFILE IN CHILDREN WITH ACUTE INFLAMMATION OF THE MIDDLE EAR ON THE BACKGROUND OF CHRONIC ACTIVE HEPATITIS

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✓ Resume

Purpose of the study-study of the cytokine profile in children with acute otitis media against the background of complex conservative treatment

Research materials and methods: We observed 55 children aged 3 to 10 years with acute otitis media. All children underwent a study for the period from 2018 to 2020, of which 35 children with acute inflammation of the middle ear against the background of chronic active hepatitis, which makes up the main group and 20 children with acute inflammation of the middle ear, which makes up the control group. In all sick children, cytokines (to determine the inflammatory processes) (IFN γ , IL-4) were determined in the peripheral blood serum. IFN γ , IL-4 were determined by enzyme immunoassay using test systems "Vector-Best" of the Russian Federation.

Results and discussion: The ratio of IFN γ / IL-4 (pro-inflammatory / anti-inflammatory cytokines or Th1 / Th2) in children with acute otitis media was 2.2. In the presence of a pronounced inflammatory process, that is, in children with acute inflammation of the middle ear, this indicator was 0.96. After carrying out immunocorrective treatment using Immun-5, (The drug is a balanced mixture of natural biologically active substances, the action of which is aimed at activating the body's immune system. The drug increases the body's resistance in inflammatory diseases. Use 1 capsule 2 times a day for 60 days. The drug manifests its effects, first of all, through the effect on the system of endogenous interferons and on the expression of cytokines functionally coupled with interferons - IL-2, IL-4, IL-6, IL-10 and IL-17). In the examined children with acute inflammation of the middle ear, IFN γ approached the control values, the content of IL-4, and after treatment did not normalize, remaining 5.5 times higher than the control group, the ratio of IFN γ / IL-4, in children with acute inflammation of the middle ear against the background of chronic active hepatitis of the main group; after treatment, this indicator decreased to 0.42.

Output:

Improvement of the clinical condition of children with acute otitis media, along with suppression of the level of the pro-inflammatory cytokine IFN γ , was accompanied by the disappearance of signs of otitis media, improvement of the general condition of children

Key words: acute otitis media, immune system, cytokines.

ЦИТОКИНОВЫЙ ПРОФИЛЬ У ДЕТЕЙ С ОСТРЫМ ВОСПАЛЕНИЕМ СРЕДНЕГО УХА НА ФОНЕ ХРОНИЧЕСКОГО АКТИВНОГО ГЕПАТИТА

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✓ Резюме

Цель исследования - изучение цитокинового профиля у детей с острым воспалением среднего уха на фоне комплексного консервативного лечения

Материалы и методы исследования: Под нашим наблюдением находилось 55 детей в возрасте от 3 до 10 лет с острым воспалением среднего уха. Всем детям проведено исследование за период с 2018 по 2020 года, из них 35 детей с острым воспалением среднего уха на фоне хронического активного гепатита который составляет основную группу и 20 детей с острым воспалением среднего уха, который составляет контрольную группу. У всех больных детей был определен цитокинов (для определения воспалительных процессов) (ИФН γ , ИЛ-4) в сыворотке периферической крови. ИФН γ , ИЛ-4 определяли методом иммуноферментного анализа с использованием тест – систем «Вектор-Бест» Российской Федерации.

Результаты: соотношение **ИФН γ /ИЛ-4** (провоспалительные / противовоспалительные цитокины или $Tx1/Tx2$) у детей с острым воспалением среднего уха равнялось 2,2. При наличии выраженного воспалительного процесса, то есть у детей с острым воспалением среднего уха этот показатель составлял 0,96. После проведения иммунокорректирующего лечения с использованием Иммун-5 (Препарат представляет собой сбалансированную смесь натуральных биологически активных веществ, действие которых направлено на активацию иммунной системы организма. Препарат повышает сопротивляемость организма при воспалительных заболеваниях. Применение по 1 капсула 2 раза в день в течение 60 дней. Препарат проявляет свои эффекты, прежде всего, через влияние на систему эндогенных интерферонов и на экспрессию функционально сопряженных с интерферонами цитокинов — ИЛ-2, ИЛ-4, ИЛ-6, ИЛ-10 и ИЛ-17). У обследуемых детей при острым воспалением среднего уха **ИФН γ** приблизился к контрольным значениям, содержания **ИЛ-4**, и после лечения не нормализовался, оставаясь в 5,5 раза выше, чем контрольной группы, соотношение **ИФН γ /ИЛ-4** у детей с острым воспалением среднего уха на фоне хронического активного гепатита основной группы- после лечения этот показатель снизился до 0,42.

Вывод: Улучшение клинического состояния детей с острым воспалением среднего уха, наряду с подавлением уровня про воспалительного цитокина **ИФН γ** , сопровождалось исчезновением признаков воспаления среднего уха, улучшением общего состояния детей.

Ключевые слова: острый воспаление среднего уха, иммунная система, цитокины.

SURUNKALI FAOL GEPATIT FONIDA O'RTA QULOQNING O'TKIR YALLIG'LANISHI BO'LGAN BOLALARDA SITOKIN KO'RSATGICHLARI

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✓ Rezyume

Tadqiqot maqsadi- kompleks konservativ davo fonida o'tkir o'rta otit bo'lgan bolalarda sitokin profilini o'rganish

Tadqiqot materiallari va usullari:

Biz 3 yoshdan 10 yoshgacha bo'lgan 55 bolada o'tkir o'rta otit bilan kuzatdik. 2018 yildan 2020 yilgacha bo'lgan davrda barcha bolalarda tadqiqot o'tkazildi, shundan asosiy guruhni surunkali faol gepatit fonida 35 nafar o'tkir o'rta otitli bolalar tashkil etdi va nazorat guruhini 20 nafar o'tkir o'rta otit bilan kasallangan bolalarni tashkil etdi. Barcha bemor bolalarda sitokinlar ko'rsatkichlari (yallig'lanish jarayonlarini aniqlash uchun) (**IFN γ** , **IL-4**) periferik qon zardobida aniqlangan. **IFN γ** , **IL-4** ko'rsatkichlari immun ferment analizi orqali Rossiya Federatsiyasining "Vektor-Best" test tizimlari yordamida aniqlandi.

Natijalar va muhokama:

O'tkir o'rta otit kasalligi bo'lgan bolalarda **IFN γ** / **IL-4** nisbati (yallig'lanish oldi / yallig'lanishga qarshi sitokinlar yoki $Th1$ / $Th2$) 2.2ga teng bo'ldi. Aniq yallig'lanish jarayoni mavjud bo'lganda, ya'ni o'rta quloqning o'tkir yallig'lanishi bo'lgan bolalarda bu ko'rsatkich 0,96 ni tashkil etdi. **Immun-5** yordamida immunokorektiv davolash o'tkazilgandan so'ng (Preparat tabiiy biologik faol moddalarning muvozanatli aralashmasi bo'lib, uning ta'siri organizmning immunitet tizimini faollashtirishga qaratilgan. Preparat organizmning yallig'lanish kasalliklariga chidamliligini oshiradi. 1 kapsuladan 2 marta kuniga 60 kun davomida ichish buyuriladi. Preparat o'z ta'sirini birinchi navbatda endogen interferon tizimiga va interferonlar bilan funktsional ravishda bog'langan sitokinnarning ekspresiyasiga ta'sir qilish orqali namoyon qiladi – (**IL-2**, **IL-4**, **IL-6**, **IL-10** va **IL-17**). O'rta quloqning o'tkir yallig'lanishi bilan tekshirilgan bolalarda **IFN γ** nazorat qiymatlariga, **IL-4** tarkibiga yaqinlashdi va davolanishdan so'ng normallashtirildi, nazorat guruhidan 5,5 baravar yuqori bo'lib, **IFN γ** / **IL-4** nisbati, asosiy guruhning surunkali faol gepatit fonida o'rta quloqning o'tkir yallig'lanishiga chalingan bolalarda; davolashdan so'ng bu ko'rsatkich 0,42 ga kamaydi.

Xulosa: O'tkir orta otit bo'lgan bolalarning klinik holatini yaxshilash, yallig'lanishga qarshi sitokin **IFN γ** darajasini pasaytirish bilan birga, o'tkir o'rta otit belgilarining yo'qolishi, bolalarning umumiy ahvoli yaxshilanishi bilan birga kechdi.

Kalit so'zlar: o'tkir o'rta otit, immunitet tizimi, sitokinlar.

Relevance

Chronic active hepatitis (CAH) occupies one of the leading places in the structure of infectious pathology. The unfavorable epidemic situation prevailing all over the world is characterized by a steady increase in the incidence of CAH in all age groups of children [2,4].

One of the reasons for the close attention of clinicians to the problem of CAH is the possibility of developing its unfavorable outcomes - damage to internal organs and damage to the tympanic cavity [7].

So, according to some authors, the presence of chronic HCV infection in approximately 25-30% of cases leads to the formation of some complications (8, 9). Mortality associated with the consequences of CAH remains high.

From a clinical standpoint, the urgency of this problem is due to the lack of informative methods for predicting an unfavorable course of the disease with insufficient effectiveness of existing treatment methods.

The solution of these problems is not possible without an in-depth study of the pathogenesis of CAH, in particular, factors that can influence the development of acute inflammation of the middle ear.

In recent years, significant progress has been made in studying the mechanisms of CAH progression. It has been established that the prognosis of an unfavorable course of CAH is largely determined by indicators characterizing the severity and rate of damage to the middle ear [6,12].

At the same time, factors such as gender, age at the time of infection, premorbid background, predisposing factors, diabetes mellitus, and intravenous use of psychoactive substances are of decisive importance in the outcomes of chronic HCV infection [1,13].

Currently, it is considered established that the concentration of a number of pro-inflammatory cytokines in the blood of sick children with CAH increases [14]. However, many questions regarding their relationship, as well as evidence of a direct involvement in the development of acute otitis media, remain unclear.

Thus, there are still many unresolved issues related to the diagnosis and, especially, the prognosis of the course, outcomes and various complications of CAH. The factors that can have an adverse effect on the rate of development of acute otitis media in children have not been fully identified and characterized. The diagnostic value of indicators for assessing acute otitis media in children requires

clarification. There are no clear recommendations on the complex use of CAH progression factors for the individual prognosis of its course, which significantly complicates the choice of an adequate tactics for managing sick children.

Acute inflammation of the mucous membrane of the middle ear - the auditory tube, tympanic cavity and cells of the mastoid process - a disease most common in childhood is a multifaceted problem. Acute otitis media (AOM) in children with chronic active hepatitis belongs to an urgent pathology and requires attention not only from otorhinolaryngologists, but also pediatricians, pediatric infectious disease specialists, allergists. So, in the classification proposed by M.Ya. Kozlov [1.3.4.10], highlighted "obvious acute otitis media", "acute otitis media in infectious diseases", "exudative-allergic recurrent otitis media".

Modern standards of examination for the treatment of patients with AOM against the background of chronic active hepatitis recommend the implementation of the proposed "therapeutic and diagnostic algorithm for pathology of LOP organs" [5,15]. However, depending on the etiopathogenesis of the disease, clinical manifestations and stage of the process, the approach to solving the issue of organizing treatment is also different (11). Our experience of observing children in a multidisciplinary regional children's hospital allowed us to develop a certain tactics for managing these sick children.

All of the above was the basis for this study.

Objective: to study the cytokine profile in children with acute otitis media against the background of complex conservative treatment.

Material and methods

For the period from January 2018 to March 2020 under our supervision there were 55 sick children aged 3 to 10 years with acute $\rightarrow \rightarrow \rightarrow$ otitis media, of which 35 children with acute inflammation of the middle ear against the background of chronic active hepatitis, which is the main group and 20 children with acute inflammation of the middle ear, which constitutes a control group. In all sick children, cytokines (for the determination of inflammatory processes) (IFN γ , IL-4) were determined in the peripheral blood serum. IFN γ , IL-4 were determined by enzyme-linked immunosorbent assay using test systems "Vector-Best" of the Russian Federation.

All examined children were examined regardless of the presence of complaints, in addition to standard research methods (general analysis of blood, urine, bacteriological and biochemical studies), we conducted an otorhinolaryngological study for all children. All examined children were routinely examined and, according to the results of the study, according to the indications, were hospitalized for adequate treatment.

Sick children received traditional antibacterial, anti-inflammatory and local therapy in a hospital setting, then immunocorrection was prescribed, for which the domestic drug Immun-5 was used (The drug is a balanced mixture of natural biologically active substances, the action of which is aimed at activating the body's immune system. The

drug increases the body's resistance to inflammatory diseases. Use 1 capsule 2 times a day for 60 days. The drug manifests its effects, first of all, through the effect on the endogenous interferon system and on the expression of cytokines functionally coupled with interferons - IL-2, IL-4, IL-6, IL-10 and IL-17). The level of cytokines (IFN γ , IL-17) in the serum of peripheral blood was studied by the method of enzyme-linked immunosorbent assay using test systems "Vector-Best" (Russia).

Result and discussion

The results of a study of pro-inflammatory and anti-inflammatory cytokines in the serum of peripheral blood in children with acute otitis media are presented in Table 1.

Table № 1.

The content of pro-inflammatory and anti-inflammatory cytokines in the examined children before and after treatment

Indicator	Control group with acute otitis media (n = 20)	The main group with acute otitis media on the background of CAH (n = 35)
ИФН γ , пг/мл	23,70+ 5,38	<u>82,80+25,07</u> 21,93+5,28
ИЛ-4, пг/мл	10,95+3,65	<u>86,08+25,72</u> 52,04+15,06

*Note. In the numerator there are data before treatment, in the denominator - after in comparison with the control group; * - $P < 0.05$.*

The analysis of the obtained results revealed the presence of significant differences between the values of the control group and the children of the main group. Thus, in healthy children, the IFN γ level was 23.70 ± 5.38 pg / ml, while in children of the main group, this indicator was 82.80 ± 25.07 pg / ml. Thus, the level of IFN γ in children with acute inflammation of the otitis media was increased by 3.5 times, which indicated the severity of the inflammatory process in the presence of purulent discharge from the middle ear.

According to the literature, activated T-lymphocytes and natural killer cells are the source of IFN γ . Among T lymphocytes, both cytotoxic CD8 + and CD4 + helper cells are producers of interferon gamma, however, when the latter differentiate into Th1 and Th2, the ability to produce interferon gamma is retained only by Th1 cells. The most important function of IFN γ is its participation in mediating the relationship between lymphocytes and macrophages and in the regulation of the ratio of the cellular and humoral components of the

immune response. Being the main product of Th1 cells, IFN γ reduces the secretory activity of Th2 cells. Thus, IFN γ enhances the development of cellular immunity and suppresses manifestations of humoral immunity. Therefore, IFN γ plays an important role in immunoregulation, being a key cytokine of the cellular immune response and an inhibitor of the humoral immune response.

The level of IL-4 in the group of children in the control group was 7.9 times lower than in the patients of the main group. It is known that interleukin-4 has been described as a stimulating factor for B-lymphocytes because it causes B-cell proliferation. It is known from the literature that the main producers of IL-4 are T-helpers of the 2nd class. IL-4 is also synthesized by mast cells and B cell lines. IL-4 suppresses the functions of macrophages and their secretion of IL-1, TNF and IL-8, while providing an anti-inflammatory effect. Thus, IL-4 is the main product of Th2 cells and stimulates their differentiation. It causes the proliferation and differentiation of B- and T-

lymphocytes, affects the development of hematopoietic cells, macrophages, natural killer cells, basophils, being a functional antagonist of cytokines produced by Th1 cells. IL-4 promotes the development of allergic reactions, has a pronounced anti-inflammatory effect [11.13]. Comparative analysis showed that the ratio of $\text{IFN}\gamma$ / IL-4 (pro-inflammatory / anti-inflammatory cytokines or Th1 / Th2) in healthy children was 2.2. In the presence of a pronounced inflammatory process, that is, in children of the main group, this indicator was 0.96. There was a pronounced imbalance in the state of the main regulatory cytokines, which was expressed by a sharp rise in the level of anti-inflammatory cytokines and suppression of pro-inflammatory cytokines, which are the main regulators of acute inflammatory conditions. Thus, in acute inflammation of the middle ear, there is a pronounced stimulation of the production of both pro-inflammatory and anti-inflammatory cytokines, which can be regarded as a necessary condition for protection against an infectious agent and the systemic damaging effect of high concentrations of pro-inflammatory cytokines. After carrying out immunocorrective treatment using Immun-5 in children, $\text{IFN}\gamma$ approached the control values. As for the content of IL-4, after treatment it did not normalize, remaining 5.5 times higher than in children of the control group.

As noted above, the ratio of $\text{IFN}\gamma$ / IL-4, in children of the main group, after treatment, this indicator decreased to 0.42.

Output

Thus, the improvement in the clinical condition of children, along with the suppression of the level of the pro-inflammatory cytokine $\text{IFN}\gamma$, was accompanied by the disappearance of signs of otitis media, an improvement in the general condition of children (on days 9-10 after standard treatment, the condition of sick children improved, headaches, ear pain, discharge from ear decreased).

However, it should be noted that the revealed change in the level of IL-4 and the violation of the ratio of pro- and anti-inflammatory cytokines indicated the presence of an immunodeficiency state, which, apparently, was manifested by the presence of complications against the background of acute inflammation of the middle ear.

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