



New Day in Medicine
Новый День в Медицине

NDM



TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal



AVICENNA-MED.UZ



ISSN 2181-712X.
EiSSN 2181-2187

6 (56) 2023

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**ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE**

*Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал*

УЧРЕДИТЕЛИ:

**БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»**

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исследовательский центр хирургии имени
А.В. Вишневского является генеральным
научно-практическим
консультантом редакции

Журнал был включен в список журнальных
изданий, рецензируемых Высшей
Аттестационной Комиссией
Республики Узбекистан
(Протокол № 201/03 от 30.12.2013 г.)

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6 (56)

2023

www.bsmi.uz

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ИЮНЬ

Received: 20.05.2023, Accepted: 30.05.2023, Published: 15.06.2023.

UDC 616.15-099:678.7:612.017.1-092.9

IMMUNOLOGICAL FEATURES IN CHILDREN WITH ACUTE MIDDLE EAR INFLAMMATORY ON THE BACKGROUND OF CHRONIC ACTIVE HEPATITIS

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✓ Resume

Purpose of the study- study of immunological characteristics in children with acute inflammation of the middle ear 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.

ИММУНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ У ДЕТЕЙ С ОСТРЫМ ВОСПАЛЕНИЕМ СРЕДНЕГО УХА НА ФОНЕ ХРОНИЧЕСКОГО АКТИВНОГО ГЕПАТИТА

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✓ Резюме

Цель исследования - изучение иммунологических особенностей 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 T χ 1/T χ 2) 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 IMMUNOLOGIK KO'RSATGICHLARI

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✓ Rezyume

Tadqiqot maqsadi: kompleks konservativ davo fonida o'tkir o'rta otit bo'lgan bolalarda immunologik xususiyatlarini 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 hepatit 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 tahlillar: 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 sitokintlarning 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 normallashtirdi, nazorat guruhidan 5,5 baravar yuqori bo'lib, IFN γ / IL-4 nisbati, asosiy guruhning surunkali faol gepatit fonida o'rta qulog'ining 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 that has developed throughout 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 adverse 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 continues to be high. From a clinical standpoint, the relevance of this problem is due to the lack of informative methods for predicting an unfavorable course of the disease with insufficient effectiveness of existing methods of treatment.

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 middle ear damage [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].

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

Thus, there are still many unresolved issues related to the diagnosis and, especially, the prognosis of the course, outcomes and various complications of CAH. Factors that can adversely affect 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 inflammation of the middle ear in children requires clarification. There are no clear recommendations on the complex use of CAH progression factors for an individual prognosis of its course, which significantly complicates the choice of an adequate management strategy for 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 is an urgent pathology and requires the attention of not only otorhinolaryngologists, but also pediatricians, pediatric infectious disease specialists, allergists. So, in the classification proposed by M.Ya. Kozlov [1.3.4.10], singled out "obvious acute otitis media", "acute otitis media in infectious diseases", "exudative-allergic recurrent otitis media".

Modern examination standards for the treatment of patients with CCA on the background of chronic active hepatitis recommend the implementation of the proposed "treatment and diagnostic algorithm for the pathology of upper respiratory tract" [5,15]. However, depending on the etiopathogenesis of the disease, clinical manifestations and the 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 has allowed us to develop a certain tactic for managing these sick children. All of the above was the basis for the present study.

The purpose of the study: to study the cytokine profile in children with acute inflammation of the middle ear against the background of complex conservative treatment.

Material and methods

For the period from January 2019 to March 2021 under our supervision there were 55 sick children aged 3 to 10 years with acute inflammation of the middle ear, of which 35 children with acute inflammation of the middle ear against the background of chronic active hepatitis, which constitutes the main group and 20 children with acute inflammation of the middle ear, which constitutes the control group. In all sick children, cytokines (to determine inflammatory processes) (IFN γ , IL-4) were determined in peripheral blood serum. IFN γ , IL-4 were determined by enzyme immunoassay 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 blood count, urine, bacteriological and biochemical studies), we conducted an otorhinolaryngological examination for all children. All examined children were routinely examined and, according to the results of the study, were hospitalized according to indications for adequate treatment.

Sick children received traditional antibacterial, anti-inflammatory and local therapy in a hospital, 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 resistance body in inflammatory diseases. Use 1 capsule 2 times a day for 60 days. The drug manifests its effects primarily through the effect on the system of endogenous interferons and on the expression of cytokines functionally associated with interferons - IL-2, IL-4, IL -6, IL-10 and IL-17). The level of cytokines (IFN γ , IL-17) in peripheral blood serum was studied by enzyme immunoassay using Vector-Best test systems (Russia).

Result and discussion

The results of the study of pro-inflammatory and anti-inflammatory cytokines in the serum of peripheral blood in children with acute inflammation of the middle ear are presented.

The analysis of the obtained results revealed the presence of significant differences between the values of the control group and children of the main group. Thus, in healthy children, the level of IFN γ 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 middle ear inflammation was increased by 3.5 times, which indicated the severity of the inflammatory process, the presence of purulent discharge from the middle ear.

According to the literature, the source of IFN γ is activated T-lymphocytes and natural killers. Among T-lymphocytes, interferon gamma producers are both cytotoxic CD8+ and helper CD4+ cells, however, when the latter differentiate into Th1 and Th2, only Th1 cells retain the ability to produce interferon gamma. The most important function of IFN γ is its participation in mediating the relationship between lymphocytes and macrophages and in regulating 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 the 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 patients of the main group. Interleukin-4 is known to be described as a B-lymphocyte stimulating factor 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 inhibits the function 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 killers, basophils, being a functional antagonist of cytokines produced by T α 1 cells. IL-4 promotes the development of allergic reactions, has a pronounced anti-inflammatory effect [11,13].

Comparative analysis showed that the ratio of IFN γ / 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 immunocorrective treatment with the use of Immun-5 in children, IFN γ approached the control values. As for the content of IL-4, after treatment it did not

normalize, remaining 5.5 times higher than in the children of the control group. As noted above, the ratio of IFN γ / IL-4 in children of the main group - after treatment, this figure decreased to 0.42.

Conclusion

Thus, the improvement in the clinical condition of children, along with the suppression of the level of the pro-inflammatory cytokine IFN γ , was accompanied by the disappearance of signs of inflammation of the middle ear, improvement in the general condition of children (on days 9-10 after standard treatment, the condition of sick children improved, headaches, pain in the ears, discharge from ear decreased).

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

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Поступила 20.05.2023