IMMUNOPATHOGENESIS OF CLINICAL MANIFESTATIONS CHRONIC RHINOSINUSITIS

Xolov X.N., Nurov U.I., Narzullaev N.U.

Bukhara State Medical Institute

Annotation. Clinical manifestations of diseases reflect the level of immune reactivity. Objective: to determine the role of immune reactivity factors in the pathogenesis of pain symptoms in rhinosinusitis.240 patients with rhinosinusitis were examined. All underwent a complete clinical examination, immunological, determination of the levels of cytokines IL-10, IL-4, IL-6, IL-8, IL-10, TNFa, INFy and substance R. Determination of the level of substance P in the patient's blood serum is a criterion for an objective assessment of the pain symptom in rhinosinusitis, its value in the range of 100 - 2000 pg /ml indicates normal neuro-immune interaction.A pronounced pain symptom in rhinosinusitis indicates neurogenic inflammation, a shift in the balance of Th1-/Th2-lymphocyte activity towards Th-1 and insufficient immune response. The absence of a pain symptom in rhinosinusitis indicates a violation of neuro-immune regulation, while the direction of differentiation of Th-l / Th-2 lymphocytes в сторону Th-2-пути, что проявляется иммунной недостаточностью.

Keywords: rhinosinusitis; pain symptom; immunodeficiency; substance R.

Clinical signs of the current course of many diseases are undergoing changes.

INTRODUCTION: The classical forms of sinusitis described in our textbooks are becoming rarer. Facial pain is no longer the main pathognomonic symptom of rhinosinusitis, as it does not reflect the severity of the disease [1.3.5]. This symptom is important and significant in the clinic, but its interpretation requires a modern reading from the point of view of molecular medicine.According to the

***e*ISSN** 1303-5150

classification, facial pain is divided into somatogenic prosopalgia, i.e. inflammatory and neurogenic pains, which include typical neuralgia of the cranial nerves and atypical prosopalgia: sympathalgia or vegetalgia. The separation of all facial pain symptoms into somatic and neurogenic is justified from the point of view of etiopathogenesis. In the clinical manifestation of rhinosinusitis, these pathogenetic mechanisms are not separable. One disease can be the cause of both the somatic and neurogenic mechanism of pain [2.4.6]. Pain as a universal symptom of tissue damage has a single mechanism of formation. The results of modern research indicate the involvement of neuro-immune mechanisms at all stages of the pathogenesis of pain symptoms [3, 4, 5]. The basis of a single universal mechanism for the occurrence of facial pain is an inflammatory reaction caused by immune factors [6]. Thus, the clinical manifestations of diseases reflect the level of immune reactivity.

The aim of the study was to determine the role of immune reactivity factors in the pathogenesis of pain symptoms in chronic rhinosinusitis.

To achieve this goal, the following tasks were set: to study the immune status of patients with different severity of pain symptoms; to find out the relationship between the individual cytokine profile of the patient and the nature of the course of the inflammatory process manifested by pain symptoms; to identify the relationship of immune disorders with the absence of pain symptoms in patients with rhinosinusitis.

Material and methods of research. The group of subjects included 240 patients with rhinosinusitis aged 15 to 81 years, who were treated at the clinic of the Department of Ear, nose and throat Diseases of BUKHMI.The average age of the patients was 34.4 ± 0.65 years. Among them, there were 132 men (55%), 108 women (45%). Inclusion criteria were patients with rhinosinusitis, accompanied by the presence and absence of a pain symptom. The exclusion criteria were allergic diseases, rhinogenic complications, concomitant chronic diseases. The patients were divided into 2 groups depending on the nature of the inflammatory process. Group 1 included patients with viral rhinosinusitis. Group 2 included patients with purulent sinusitis. The control group consisted of 32 practically healthy people with no complaints of nasal breathing disorders,

suffering from pain symptoms, without chronic diseases.

All patients underwent a complete clinical examination, including the collection of complaints and anamnesis, examination, endoscopy of ENT organs, computed tomography of the paranasal sinuses. The facial pain symptom was assessed using a "Multidimensional verbal-color pain test" [7.9.11.13.15.17.19.21]. The immunological study included an assessment of the cellular, humoral link and phagocytosis indicators, a total of 16 parameters. Additionally, the levels of cytokines IL-1ß, IL-4, IL-6, IL-8, IL-10, TNFa, INFy and the level of substance P in the blood serum of patients were determined by enzyme immunoassay.

The results of our own research and their discussion.

Proceeding from the position that the pain symptom is not a marker of disease activity, and all pain studies are subjective [8, 9], we conducted a study of the level of substance P (SP) in the blood serum of patients as the main neurotransmitter involved in the mechanisms of pain sensitivity of the respiratory tract [10]. With the help of ROC analysis, we found SP levels that no longer correspond to the clinical signs of the disease, but indicate a violation of neuro-immune mechanisms. The diagnostic point of separation of the level of SP in the blood serum, the excess of which is associated with the neurogenic component of pain, was the value of 2000 pg/ml. The diagnostic point of separation of the level of SP in the blood serum, at which a further decrease is associated with a violation of neuro-immune interactions, was the value of 100 pg/ml.

With a moderate pain symptom characteristic of diseases of the paranasal sinuses, the level of SP in the blood serum of patients was in the range of 100-2000 pg/ml. When conducting a correlation analysis of ranked SP level indicators in patients with 100<SP<2000 pg/ml, there is a direct statistically significant relationship between the values of the SP level and the degree of activity of the inflammatory process (according to clinical signs and the level of C-reactive protein).

An ultra-high level of SP>2000 pg/ml is manifested by a pronounced pain symptom and indicates the involvement of neurogenic mechanisms in the inflammatory process. The pronounced pain symptom (SP>2000 pg/ml) does not correspond to the activity of the inflammatory process. Neurogenic

inflammation involving SP is not a typical pain symptom of the type of neurogenic pain, while it is possible that pain acts as a damaging factor and aggravates the existing inflammation initiated by an infectious agent, or the inflammatory process is provoked by pain mediators without the participation of an infectious factor.

The absence of a pain symptom at SP <100 pg /ml indicates an insufficient mediator response to the infectious factor, while the body's protective reactions do not work, which is manifested by the absence of pain. Severe inflammatory process in these patients is accompanied by a deficiency of SP. The study of immunological parameters in patients in subgroups with catarrhal and purulent process did not provide new information. The average values of most indicators corresponded to the changes characteristic of this pathology in our region. Therefore, in our study, we divided patients into subgroups depending on the level of SP in the blood serum.

With a typical pain symptom (100<SP<2000 pg/ml), changes in the immunogram parameters in group 1 with catarrhal inflammation were characteristic of a normal immune response to a viral antigen. In patients with SP>2000 pg/ml, the immunogram indicators indicate a cytotoxic variant of the immune response against the background of a deficiency of the humoral link and phagocytosis. There is a decrease in the immunoregulatory index, an increase in the absolute and relative number of NK cells. At low values of SP<IOO, the immunogram indicators revealed immunodeficiency in all directions: the cellular link, humoral and phagocytosis suffer.

In patients with catarrhal inflammation and a level of 100<SP<2000 pg/ml, virus-induced changes and cytokine profile were detected, which corresponds to the literature data [12.14.16.18.20.21]. At the same time, the immune reaction develops along the Th-1-type pathway, which is manifested by an increased level of IL-1 β and INFy. At high values of SP>2000 pg/ml, the cytokine balance is shifted towards proinflammatory cytokines.TNFa induces the synthesis of SP by sequential induction of IL-1ß [10], and IL-lß itself is a mediator of hypersensitivity of iociceptors in inflammation. In human macrophages, proinflammatory cytokines IL-10, IL-6, IL-8 and TNFa increase the expression of SP receptors [10].

At low values of SP<100, the cytokine balance indicates a shift in the direction of

*e*ISSN 1303-5150

differentiation of T-helpers towards the Th-2 pathway, and consequently to a deficiency of the cellular link of the immune response. Low concentrations of proinflammatory cytokines do not stimulate the pain symptom. The lack of an effective T-cell response may be due to an imbalance in cytokine production.With a typical pain symptom (100<SP<2000 pg/ml), changes in the immunogram parameters in group 2 with purulent inflammation of the mucous membrane were characteristic of a normal immune response to bacterial antigen.

In patients with SP>2000 pg/ml, immunogram indicators indicate a cytotoxic variant of the immune response against the background of a deficiency of the humoral link. There is a decrease in the immunoregulatory index, an increase in the absolute and relative number of CD8+ and NK cells. At SP<100 pg/ml, immunogram indicators revealed immunodeficiency in all directions. In group 2 with a typical pain symptom (100<SP<2000 pg/ml)The cytokine balance is shifted towards proinflammatory cytokines, which confirms the activation of Th-2-mediated immune mechanism.

At high values of SP>2000 pg/ml and severe pain, the reaction follows the Th-1 pathway. The pain symptom is maintained. And there is no adequate immune response. Consequently, the shift of the cytokine balance towards pro-inflammatory cytokines increases the pain symptom, and towards anti-inflammatory - weakens. The course of the disease is burdened by the mechanisms of neurogenic inflammation, which, of course, is the reason for the aggravation of the clinical picture of diseases of both infectious and non-infectious nature. What was the trigger mechanism - an imbalance of cytokines or a malfunction in the neurotransmitter system - is not yet clear, we can only assume that these disorders mutually reinforce each other, closing a "vicious circle".

At low values of SP<100, the balance is shifted towards anti-inflammatory cytokines, which reduce the production of pro-inflammatory cytokines. IL-10 and INFy receptors use the same signal pathway and can activate the same transcription factors. Therefore, it is possible that IL-10 may reduce the expression of SP (NK.-1-receptor) receptors. IL-10 reduces the activity of the inflammatory process and, apparently, reducing the concentration of SP, reduces the pain symptom. In these patients, the mechanisms of differentiation

of T-lymphocytes are disrupted: the concentration of IL-4, necessary for the development of a humoral Th-2-mediated immune response, is reduced, and, at the same time, the concentration of INFy, necessary for the stimulation of the cellular Th-1 pathway of immunity, is reduced.

Conclusions:

1.A pronounced pain symptom in rhinosinusitis indicates neurogenic inflammation characterized by a level of substance P in the blood serum of more than 2000 pg /ml, a sharp shift in the cytokine balance towards proinflammatory cytokines, the balance of activity of Th 1-/ Th2-lymphocytes towards Th-1 and insufficient immune response.

2. The absence of a pain symptom in rhinosinusitis with a serum level of substance P less than 100 pg/ml indicates a violation of neuro-immune regulation, while the cytokine balance is predominantly shifted towards anti-inflammatory cytokines, and the direction of differentiation of Th-l/Th-2 lymphocytes towards the Th-2 pathway, which is manifested by immune insufficiency, which leads to a severe or prolonged course of the inflammatory process.

LIST OF LITERATURE.

1.Нарзуллаев Н.У. Опыт лечения отоантритов у ВИЧ-инфицированных детей // Журнал теоретической и клинической медицины. - Ташкент, 2010. - №6. - С. 86-88. (14.00.00; №3).

2.Гариб В.Ф, Хасанов С.А., Нарзуллаев Н.У. Особенности антибактериальной терапии у ВИЧ-инфицированных детей с острым средним отитом // Журнал теоретической и клинической медицины. - Ташкент, 2010. - №5. - С. 115-118. (14.00.00; №3).

3.Нарзуллаев Н.У., Нуров У.И., Пардаев М.С. Эпидемиологическая характеристика заболеваемости ЛОР-органов у ВИЧ-инфицированных детей // Стоматология. – Ташкент, 2010. - №3-4, - С. 29-31. (14.00.00; №12).

4.Нарзуллаев Н.У., Вохидов Н.Х., Раджабов Р.Р. Особенности течения острого среднего отита у детей инфицированных вирусом иммунодефицита человека // Стоматология. - Ташкент, 2010. - №3-4. - С. 89-90. (14.00.00; №12).

5.Нарзуллаев Н.У. Стартовая антибиотикотерапия при остром среднем отите и остром синусите у ВИЧ-инфицированных детей // Инфекция,

иммунитет и фармакология. - Ташкент, 2010. - №5. - С.45-48. (14.00.00; №15).

6.Нарзуллаев Н.У. Клинико-иммунологические особенности течения острого среднего отита у ВИЧ-инфицированных детей в зависимости от путей инфицирования // Инфекция, иммунитет и фармакология. – Ташкент, 2010. - №5. - С. 49-51. (14.00.00; №15).

7.Нарзуллаев Н.У., Ахмедов А.Т., Хомидов Ф.К. Микозы в структуре оппортунистических заболеваний полости рта и глотки у ВИЧ-инфицированых детей // Журнал теоретической и клинической медицины.– Ташкент, 2011. - №3. – С. 115-117. (14.00.00; №3).

8.Нарзуллаев Н.У., Хомидов Ф.К., Ахмедов А.Б. Местная терапия воспалительной патологии глотки у ВИЧ-инфицированных детей // Инфекция, иммунитет и фармакология. – Ташкент, 2011. - №1-2. - С. 249-253. (14.00.00; №15).

9.Нарзуллаев Н.У., Хасанов С.А., Хомидов Ф.К. Иммунные нарушения у новорожденных и грудных ВИЧ-инфицированных детей с острым средним отитом // Инфекция, иммунитет и фармакология. – Ташкент, 2011. - №1-2. - С. 254-258. (14.00.00; №15).

10.Нарзуллаев Н.У. Микозы в структуре оппортунистических инфекций среднего уха у ВИЧ-инфицированых детей // Инфекция, иммунитет и фармакология. – Ташкент, 2011. - №7. - С. 56-58. (14.00.00; №15).

11.Нарзуллаев Н.У. Клиника и течение острого среднего отита у ВИЧ-инфицированных детей // Инфекция, иммунитет и фармакология. – Ташкент, 2011. - №7. - С. 59-61. (14.00.00; №15).

12.Нарзуллаев Н.У. Острый средний отит у ВИЧ-инфицированных детей // Проблемы биологии и медицины. – Самарканд, 2012. - №1(68). - С. 92-93. (14.00.00; №19).

13.Нарзуллаев Н.У. Роль микрофлоры у ВИЧ-инфицированных детей в этиологии хронического тонзиллита // Проблемы биологии и медицины. – Самарканд, 2012. - №1(68). - С. 94-96. (14.00.00; №19).

14. Narzullaev N.U. The Incidence of exudative otitis media in HIV-infected children //International Journal BIOMEDICINE (IJBM) USA 2012.-№1. - P.211-213. IF- 0,654.

15. Narzullayev N.U., Suleymanov S.F., Ismailova A.A., Sabitova R.Z. Immune Status of HIV-positive Children with Acute Rhinosinusitis // International

*e*ISSN 1303-5150

Journal of Public Health Science (IJPHS) USA. – 2013. - Vol. 2, №3. - P. 83-88. IF-1,966.

16.Нарзуллаев Н.У., Вохидов Н.Х., Раджабов Р.Р., Адилова Г.М., Нуров У.И. Эффективность применения амоксиклава с рокситромицином при лечении воспалительных заболеваний ЛОР-органов у ВИЧ-инфицированных больных // Биология ва тиббиёт муаммолари. – Самарқанд, 2013. - № 4.1. - 72-73б. (14.00.00; №19).

17.Нарзуллаев Н.У., Вохидов Н.Ҳ., Раджабов Р.Р., Адилова Г.М., Нуров У.И. Характеристика цитокинов у ВИЧ-инфицированных детей с острым риносинуситом // Биология ва тиббиёт муаммолари. – Самарқанд, 2013. - № 4.1. - 74-75б.(14.00.00; №19).

18.Нарзуллаев Н.У., Сулейманов С.Ф. Характеристика иммунного статуса у ВИЧ-инфицированных детей с острым риносинуситом // Международный журнал иммунопатологии, аллергологии, инфектологии. – 2013. №1. - С. 59-63.(14.00.00 №55).

19. Narzullayev N. U. The characteristic of the immune status at HIV-infected children with acute rhinosinusitis // European Science Review. - Austria, 2015. - № 7-8. - P. 85-89. (14.00.00; №19)

20.Нарзуллаев Н.У, Сулейманов С.Ф. Параметры иммунного статуса у ВИЧ-инфицированных детей с острым риносинуситом // Журнал инфектологии.- Санкт-Петербург, 2017.-С.24-28. (14.00.00; №162).

21. Narzullayev N.U. Far GALS efficiency in complex treatment of HIV-infected children with acute purulent sinusitis // European Science Review . Austria, 2017 №1-2 P.86-88.(14.00.00; №19)