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FUNCTIONAL STATUS OF IMMUNE STATUS IN INFLAMMATORY DISEASES OF THE PARANASAL SINUSES IN TWIN CHILDREN

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ABSTRACT

The Aim of this work was to study the functional activity of monocytes, neutrophils and cytokines in twin children with Inflammatory diseases of the paranasal sinuses in comparison with non-twins. It was found that with various rhinosinusitis in children, phagocytic activity of monocytes in blood decrease, which causes the development of a chronic purulent focus and is characterized by an increase in monocytes with viral inclusions. In patients with Inflammatory diseases of the paranasal sinuses, the activity of non-specific protective factors of the body is significantly reduced, which is expressed in a decrease phagocytic activity of monocytes and an increase monocyte with viral inclusions, which is more evidently in twin children than in non-twin children. Serum cytokines in children with Inflammatory diseases of the paranasal sinuses were significantly increased in relation to the data of healthy children. In children-twins and non - twins, the parameters of anti-inflammatory cytokines changed in different directions.

Keywords: twin children, cytokines, non-specific protective factors, inflammatory diseases of the paranasal sinuses

INTRODUCTION

Inflammatory diseases of the paranasal sinuses (IDPS) - an actual problem of practical otorhinolaryngology. The frequency of this pathology is indicated by the fact that among patients treated in otorhinolaryngological hospitals, from 15 to 36% are people suffering from sinusitis [7;8]

In the first place in terms of the frequency of lesions is the maxillary (maxillary sinusitis), then the ethmoidal (ethmoiditis), frontal (frontitis), sphenoid (sphenoiditis)

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paranasal sinuses. This sequence is typical for adults and children over 7 years of age. Children under the age of 3 years are dominated by ethmoiditis (up to 80-92%), from 3 to 7 years of age ethmoiditis and maxillary sinusitis.

It is necessary to take into account that twins are born prematurely, among them the stillbirth rate is high, and the infant mortality rate is higher. The level of intelligence among twins is lower than among single-born [5].

But there are few and scattered materials on the study of the factors of protection of the body of twins in IDPS in a comparative aspect.

It is known that monocytes destroy foreign microorganisms, damage their own cells, participate in the regulation of the formation of other immunocompetent cells, present information about the antigen to lymphocytes, and differentiate tissue macrophages from them [1;6].

There is information from Matkarimova M. Yu. et al. [4] on the phagocytic activity of monocytes in patients with IDPS, but unfortunately, there are practically no studies on the study of their functional activity in IDPS in twin children in comparison with non-twins.

In this regard, the aim of this research work was to study the functional activity of monocytes, neutrophils, and cytokine status in patients with IDPS.

MATERIALS AND METHODS

To achieve this goal, studies were conducted in 122 children-twins and non-twins from 7 to 18 years old, permanently residing in the Bukhara and Navoi regions of Uzbekistan. All the sick children were hospitalized and received treatment in Bukhara and Navoi regional multidisciplinary medical centers.

All examined children were divided into 4 groups: group 1-twin children with IDPS (n=45); group 2-non-twin children with IDPS (n=45); group 3 - healthy twins without IDPS (n=16); group 4 - healthy non-twins without IDPS (n=16).

The first group was divided into 3 subgroups depending on nosological units: 1a subgroup - 15 twin children with chronic purulent maxillary sinusitis (ChPMS); 1b subgroup - 15 twin children with chronic rhinosinusitis (ChR); 1c subgroup-15 twin children with chronic frontitis (ChF).

The second group was also divided into 3 subgroups on the same basis: 1a subgroup - 15 twin children of ChPMS; 1b subgroup-15 twin children of ChR; 1c subgroup - 15 ChF twin children.

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Methods of rhinoscopy, otoscopy, pharyngoscopy, direct laryngoscopy and digital radiography were used to verify the diagnosis. All diagnoses were confirmed by conventional microbiological methods (Bergy's Manual of Microbiology, 1997).

The functional activity of monocytes in vitro was determined by the phagocytic activity of monocytes (FAM) and the detection of viral inclusions in monocytes (VIM) in 122 patients and healthy and sick children-twins and non-twins.

FAM was determined in vitro in the nitroblue tetrazole recovery test (NTR-test) by Filev L. V. et al. (1985). The percentage ratio of FAM reflecting the intensity of phagocytosis and its completeness due to the activity of phagosome oxidases was revealed [2]. Antiviral resistance of monocytes was determined by the detection of VIM. The percentage of monocytes with viral inclusions was calculated [3].

The NTR-test evaluates the activity of phagocytes that are able to absorb foreign pathogens. The NTR-test characterizes the redox potential of monocytes and neutrophils. The test is based on pinocytosis of a monocyte or neutrophil activated NTR solution and the transformation of a soluble, colorless NTR into an insoluble dark blue formosan, which was determined using a microscope (manufactured in Germany) under an immersion system (magnification 90x10=900 times). To do this, a drop of blood of the examined child on a slide was mixed with a solution of NTR, incubated in a thermostat (manufactured in the Russian Federation) at 37^0C for 30 minutes. Then, the number of monocytes containing formazan granules was counted in the stained smear [4].

Spontaneous NTR-test-oxygen dependent phagocytosis, which characterizes the degree of activation of antibacterial oxygen-dependent systems within the phagocyte allows you to assess the readiness of the cell to "digest" the foreign antigen.

Induced NTR test - phagocytosis in the presence of stimulants (zymosan), which allows to assess the readiness of the cell for "digestion" of foreign antigen. Characterizes the reserve capabilities of oxygen-dependent intracellular systems.

The phagocytic activity of neutrophils (PAN) reflects the ability of neutrophils to recognize and capture microorganisms. Phagocytic reserve is the ratio of a spontaneous NTR-test to an induced one. It is used to identify the reserve capabilities of intracellular systems of the mononuclear-phagocytic system. In the study of oxygen-dependent biocidicity of neutrophils, the NTR- test was also used (Park et al., 1968, modified by Mayanskiy D. N., 1983). The functional reserve of neutrophils of the examined children was determined by an induced NTR-test (Bachner, 1987). As

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an inducer, zymosan in the form of a suspension (1 mg/ml) and a biopolymer of the yeast shell *Sacchoromyces cerevisi* were used.

The cytokine status of patients with IDPS and healthy children was assessed by determining by increasing of inflammatory (interleukin-6, interleukin-8) and anti inflammatory (interleukin-4) cytokines. Interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-4 (IL-4) were determined in the blood serum of examined patients with IDPS and healthy twin children, as well as non-twins, using immunoenzyme analise (IEA). For this purpose, used the test "Cytokine", RF [5].

Statistical processing of the material was carried out by conventional methods of variation statistics using computer programs for biomedical research.

RESULTS AND DISCUSSION

It is established that in healthy twin children (3-group) the FAM is 25.7±0.9%, and the children are not twins (4-group), this parameter was not statistically significant, but significantly higher at 27.3±1,1% (table 1). In children twins with IDPS noted significant decrease of this index relative to group 3 (control), as patients with ChPMS (subgroup 1a), a decline of 2.49 times to 10.3±0.9%, and with ChR (subgroup 1b) 2.34 times to 11.0±0.7%, and with ChF (subgroup 1c) 1.72 times - up to 14,9±0,8% ($P<0.001$). In the examined patients with non-twin IDPS in comparison with the control group (group 4), there were also significant differences ($P<0.05$), but the difference was not as pronounced as in the patients with twin children. Thus, the data of subgroup 2a (ChPMS) differed from the control data by 2.24 times - up to 12.2±1.0%, subgroup 2b (ChR) by 2.07 times - up to 13.2±0.9%, subgroup 2c (ChF) by 1.66 times - up to 16.4±1.0% ($P<0.001$). Thus, it was established that in patients with IDPS, both twins and non - twins, there was a significant decrease in FAM in relation to these control groups ($P<0.05$-$P<0.001$), which is confirmed by a relatively low multiplicity of differences from the control values. But the analysis shows that the intensity of the decrease in this indicator was greater in twin children than non-twin children, and this is manifested in different pathologies (ChPMS, ChR, ChF) almost equally. The results obtained prove that the nonspecific protection factor FAM suffers more in twin children than in single-born children.

Table 1. Indicators of functional activity of blood monocytes of twin children with various rhinosinusitis

Study groups	FAM, %	VIM, %
Group 3, n=16	25,7±0,9	6,1±1,0
Group 4, n=16	27,3±1,1	7,8±1,2

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1a subgroup, n=15	10,3±0,9* ↓	33,7±1,8* ↑
2a subgroup, n=15	12,2±1,0* ↓	28,1±1,5* ↑
1b subgroup, n=15	11,0±0,7* ↓	33,7±1,5* ↑
2b subgroup, n=15	13,2±0,9%* ↓	27,8±1,9* ↑
1c subgroup, n=15	14,9±0,8* ↓	26,7±1,9* ↑
2c subgroup, n=15	16,4±1,0* ↓	23,1±2,0* ↑

Note: * - a sign of the reliability of differences in the indicators of sick children compared to healthy children; ↓, ↑ - the direction of changes.

A significant decrease in FAM is observed in all patients with twin children with ChPMS, ChR, and ChF, but it is less intense in patients with ChF than other studied pathologies (P<0.05).

The trend of changes was also preserved in the study of VIM. If viral inclusions were detected in monocytes of healthy non-twins (group 4) in 7.8±1.2% of cases, in healthy twins (group 3) this indicator was slightly reduced to 6.1±1.0% (P>0.05). The intensity of the increase in this parameter was significantly greater in patients with twin children with IDPS compared to patients with non-twin children with this pathology (P<0.05).

Thus, in subgroup 1a (ChPMS) the increase was 5.52 times (respectively 33.7±1.8% vs. 6.1±1.0%, P<0.001), while in subgroup 2a the increase was 3.60 times (respectively 28.1±1.5% vs. 7.8±1.2%, P<0.001). Almost the same parameters were obtained for other pathological conditions-respectively, in 1b and 2b subgroups (ChR), the increase was 5.39 and 3.56 times, and in 1b and 2b subgroups (ChF) 4.38 and 2.96 times (P<0.05).

In patients with twins with ChR, there is a sharp increase in the percentage of VIM to 33.7±2.8%, which is 4.32 times more than the indicators of the control group (7.8±1.2%) - P<0.001.

Similar results were obtained in patients with ChPMS (32.9±3.5%) and ChF (26.7±3.9%), although the intensity of the lesion in the latter was lower than in other pathologies (P<0.05).

Thus, in contrast to FAM, the reverse picture was obtained when determining VIM-there were more viral inclusions in monocytes in twin children with IDPS than in non-twin children. But the intensity (multiplicity) of differences compared to healthy children was greater in twins, which proves that the pathological process is more pronounced and noticeable in them. This fact suggests that when developing an algorithm for the management and treatment of sick children in the IDPS, it is necessary to take into account this pattern that we have identified.

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The results obtained allowed us to conclude that in various studied IDPS, FAM decreases, which causes the development of a chronic purulent focus and creates conditions for intracellular persistence of various viruses. In addition, viral damage to monocytes suppresses their functional activity, as a result of which their contribution to the specific and non-specific resistance of the body of children, especially twins, is reduced.

The next stage of research was to study the oxygen-dependent reactivity of neutrophils in the examined children-twins and non-twins of patients with IDPS.

The initial indicators of oxygen-dependent neutrophil reactivity in all groups reflected a decrease in the spontaneous NTR-test compared to the data of healthy children of the 3rd and 4th control groups (table 2).

Table 2. Indices of the oxygen-dependent biocenosi of neutrophils in twin children with rhinosinusitis, ed.

Study groups	Spontaneous NTR-test	Induced nst-test	Stimulation index
Group 3, n=16	9,8±0,8	20,8±1,1	2,2±0,4
Group 4, n=16	10,8±0,9	23,6±1,2	2,2±0,5
1a subgroup, n=15	6,3±0,7* ↓	20,1±1,3 ↓	3,2±0,5
2a subgroup, n=15	7,4±0,6* ↓	22,3±1,2 ↓	3,0±0,4
1b subgroup, n=15	5,2±0,6* ↓	15,9±1,2* ↓	3,1±0,4
2b subgroup, n=15	7,1±0,8* ↓	20,8±1,1* ↓	2,9±0,5
1c subgroup, n=15	7,7±0,8* ↓	20,4±1,0 ↓	2,9±0,4
2c subgroup, n=15	8,5±0,9* ↓	23,8±1,2 ↑	2,8±0,5

Notes: * - a sign of the reliability of differences in the indicators of sick twin children from those of healthy children;↓, ↑ - the direction of changes.

This was most characteristic in twin children with ChPMS (1a-subgroup) and CHR (1b-subgroup), where the decrease in the spontaneous NTR-test parameter was 1.5-and 1.9-fold (respectively 6.3±0.7 units and 5.2±0.6 units versus 9.6±0.8 units, $P<0.001$).

In patients with ChF (subgroup 1b), the decrease was less noticeable (by 1.3 times-7.7±0.8 units, respectively, versus 9.6±0.8 units), but significant. The results obtained indicate that the oxygen-dependent biocides of neutrophils significantly decreases in patients with IDPS compared to healthy children. This fact confirms that the PAN significantly decreases in patients with twin children with IDPS, which in turn leads to a decrease in the nonspecific resistance of the body of the examined patients.

In patients with non-twin children, the same trend was maintained, where the parameters of sick children were significantly reduced in relation to the control data

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(group 4, P<0.05). However, the intensity of the changes was noticeably lower than in the twin children of patients with IDPS. This fact proves that in the pathology of the paranasal sinuses in single-born children, the nonspecific resistance of the body suffers less than in twin children, which is confirmed by the results obtained. The results of the induced NTR-test showed a different picture. When stimulated with zymosan, all the studied indicators increased in almost all examined healthy and sick children. It should be noted that the parameters of sick children reached the level of control values and did not differ significantly from them (P>0,05). The degree of stimulation was 2.2 or more times, as evidenced by the parameters of the stimulation index. It should be emphasized that in sick children, the stimulation index was higher than in healthy children, and the same in both twins and non-twins. The stimulation index of sick children ranged from 2.8±0.5 to 3.2±0.6 units, which is more than in healthy children (2.2±0.4 units).

The results obtained indicate that the reserve of functional activity of neutrophils is high in patients with IDPS, regardless of the fact that the children were twins or non-twins. In this regard, the obtained results suggest that despite the presence of a pathological focus in the body, it is possible to restore the reduced potential of neutrophil activity by correcting drugs that increase the activity of non-specific resistance factors of the body.

Thus, the oxygen-dependent reactivity of neutrophils, which characterizes the nonspecific resistance of the body, decreases in the pathology of the paranasal sinuses, which is characterized by a decrease in the spontaneous NTR-test. An increase in the induced NTR-test after stimulated by zymosan indicates the reserve of PAN and the potential of non-specific factors of the body's defense, although the spontaneous NTR-test shows that functional activity decreases more in twin children than in non-twin children. But the functional reserve was the same in twin and non-twin children.

It was found that the determination of pro-and anti-inflammatory cytokines in the blood serum of the subjects provides sufficient information for early diagnosis and management of patients in the dynamics of the course of the disease, as well as predicting the outcome of various diseases, including IDPS. This involves determining the content of pro-and anti-inflammatory cytokines when assessing the immune status in sick children [7].

Determination of the concentration of pro - and anti-inflammatory cytokines in the blood serum of children, which occupy the main place during the inflammatory process in the mucous membrane of the paranasal sinuses. It is known that the

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causative agent of IDPS causes a pathological process only if it was able to overcome the "first echelon of protection", represented by non-specific factors of resistance of the body. In this case, epithelial cells can cause, spread and modulate inflammation. They are able to secrete pro-inflammatory cytokines (IL-6, IL-8) that attract inflammatory cells [5].

The results of measuring the concentration of cytokines in the blood serum of twin and non-twin children showed that, despite the noticeable heterogeneity of the results obtained within each group, patients with IDPS showed an increase in the values of IL-6 and IL-8 compared to children of the control group, as well as a tendency to increase the level of IL-4 (table 3).

Thus, the study of pro-and anti-inflammatory cytokines in patients with IDPS of twin and non-twin children showed that in sick children of both groups (groups 3 and 4), both types of cytokines were significantly increased in relation to the data of healthy children. In addition, it should be noted that proinflammatory cytokines (IL-6 and IL-8) were significantly elevated in twin children in relation to non-twin data, the reverse picture was observed when studying the parameters of anti-inflammatory cytokines (IL-4), where the data of sick non-twin children were in relation to the indicators of twin children ($P<0.05$).

Table 3. Comparative content of pro-and anti-inflammatory cytokines in twin and non-twin children with IDPS, M±m

Groups	ИЛ-8	ИЛ-6	ИЛ-4
Group 3, n=16	10,1±0,3	7,4±0,3	9,0±1,0
Group 4, n=16	10,4±0,2	7,3±0,5	9,2±1,0
1a subgroup, n=15	45,7±0,3* ↑	65,1±0,9* ↑	73,6±1,1* ↑
2a subgroup, n=15	40,3±0,4* ↑	59,6±0,8* ↑	79,3±1,0* ↑
1b subgroup, n=15	42,6±0,2* ↑	68,5±0,8* ↑	70,2±1,2* ↑
2b subgroup, n=15	36,8±0,5* ↑	61,2±0,9* ↑	78,6±1,1* ↑
1c subgroup, n=15	6,7±0,3* ↑	23,3±0,9* ↑	9,8±1,3* ↑
2c subgroup, n=15	11,5±0,2* ↑	28,7±0,9* ↑	14,5±1,2* ↑

Notes: * - a sign of the reliability of differences in the indicators of sick twin children from those of healthy children;↓, ↑ - the direction of changes.

CONCLUSION

1. With various rhinosinusitis in children, blood FAM decreases, which causes the development of a chronic purulent focus and forms conditions for intracellular persistence of viruses, which is characterized by an increase in monocytes with viral inclusions.

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2. In patients with IDPS, the activity of non-specific protective factors of the body is significantly reduced, which is expressed in a decrease in FAM indicators and an increase in monocytes with viral inclusions in vitro, which is more pronounced in twin children than in non-twin children.

3. Serum cytokines in patients with IDPS were significantly elevated in relation to the data of healthy children, it was also noted that the parameters of pro-and anti - inflammatory cytokines varied in different directions in children-twins and non-twins.

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