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CYTOKINE PROFILE IN CHILDREN WITH CONGENITAL CLEFT LIP AND PALATE

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ABSTRACT

Background: It was found that in recent years all over the world is progressively increasing the number of children with congenital malformations, including the face and jaws. The problem of changing the state of the immune system in children with CCULaP little studied. In postnatal adaptation of the immune system of newborn children by one of the leading mechanisms is the activation of cytokine system, which play an important role in protecting, launching immune processes. **Objective:** The study of the role of serum cytokines and their diagnostic significance in children with congenital cleft lip and palate to support new approaches to rehabilitation and prevention of complications at various stages of treatment. **Methods:** The material for the research was the peripheral blood of 210 children with congenital cleft lip and / or palate, are at different stages of surgical treatment at the Department Children's Maxillofacial Surgery Regional Hospital of Bukhara. Sick children were 3 groups depending on the type of cleft: 1st group - 55 children with congenital cleft upper lip, 2nd group - 75 children with congenital cleft palate and third group - 80 children with congenital cleft lip and palate. **Result:** Thus, it is shown pathogenetic role and diagnostic value of the studied cytokine (IL-4, IL-6, IL-18 and MCP-1) in children with congenital cleft lip and palate, the severity of which can be a criterion for the degree of violation remodeling process bone, that must be considered when carrying out surgical treatment in this group of children

KEYWORDS: Children, congenital cleft lip and / or palate, cytokines.

INTRODUCTION

It was found that in recent years all over the world is progressively increasing the number of children with congenital malformations, including the face and jaws.[1,2,4,6] In particular, congenital cleft lip and palate - account for about 13% of all congenital malformations of human development.[2,4,7] Congenital vices maxillofacial area in relation to their frequency, severity anatomical and functional disorders, social difficulties adaptation of patients, are the economic aspects of a the most important medical problems.[3,8,9]

The prevalence of congenital malformations of human development is a characteristic of the state of health of the population. According to the average WHO frequency birth with cleft lip and palate children is 1: 750 newborns (in Russia this figure ranges from 1: 1000 to 1: 600 in different regions in Uzbekistan - from 1: 1200 to 1: 600) that 20-30% of all human development defects and 86% of malformations maxillofacial (Chloe).[5,6]

The severity of the defect development Face due not only to external disfigurement, pronounced functional impairment, social handicap child in preschool and school teams, conflict tension and negative psychological background in the family, but also by the fact that deformation causing somatic disorders, leading to braking growth and underdevelopment of the child's body in general.[5,8,9]

Continuing anatomical abnormalities cause disruption of the directly affected and related bodies with them. Disturbed the harmony of a few areas, there are the so-called Co-secondary deformation. Features of mental conditions of children are very different from the norm, as organic character changes lead to unpredictable neurotic reactions associated with asthenic syndrome and vascular dystonia whole organism.[3,5]

One important reason for the pathological processes of the maxillofacial region are in violation of the various parts of the immune system. The problem of changing the state of the immune system in children with CCULaP little studied. In postnatal adaptation of the immune system of newborn children by one of the leading mechanisms is the activation of cytokine system, which play an important role in protecting, launching immune processes. Study levels of cytokines that regulate individual development and physiological functions of the body's protective response [4,5, 7, 8], provides information on the functional activity of the cells, the

stage of the inflammatory process and its severity, the ratio of activation of cytokine-producing T-lymphocytes, which is of great diagnostic and prognostic value.[4,5,6,7]

Research objective - the study of the role of serum cytokines and their diagnostic significance in children with congenital cleft lip and palate to support new approaches to rehabilitation and prevention of complications at various stages of treatment.

The aim of the study. To evaluate the role of immunobiological regulation and molecular genetic mechanisms in the formation of congenital cleft upper lip and palate.

MATERIALS RESEARCH METHODS

The material for the research was the peripheral blood of 210 children with congenital cleft lip and / or palate, are at different stages of surgical treatment at the Department Children's Maxillofacial Surgery Regional Hospital of Bukhara. Sick children were 3 groups depending on the type of cleft: 1st group - 55 children with congenital cleft upper lip, 2nd group - 75 children with congenital cleft palate and third group - 80 children with congenital cleft lip and palate. These groups of children were divided into 3 groups according to age. In the group with congenital cleft upper lip: 1st subgroup - up to 1 year, n = 18; 2nd subgroup - from 1 to 3 years, n = 22; 3rd subgroup - from 3 to 6 years, n = 15. In the group with congenital cleft palate: the 1st subgroup - up to 1 year, n = 14; 2nd subgroup - from 1 to 3 years, n = 24; 3rd subgroup - from 3 to 6 years, n = 37. In the group with congenital cleft lip and palate: the 1st subgroup - up to 1 year, n = 43; 2nd subgroup - from 1 to 3 years, n = 25; 3rd subgroup - from 3 to 6 years, n = 12.

Control groups consisted of practically healthy children of the appropriate age range. The concentration of cytokines peripheral blood (IL-4, IL-6, IL-18 and MCP-1) were determined by enzyme immunoassay (ELISA) analyzer ASCENT (Finland) using test systems (ZAO "Vector-Best", Novosibirsk, Russia) .Statistic processing of the results was carried out by «Microsoft Excel» software, «StatPlus 2009". Significance of differences was determined at p <0,05.

RESULTS AND DISCUSSION

Analysis of the pro- and anti-inflammatory cytokines in children with congenital cleft lip and palate revealed the following features depending on the age range. In our studies, in the group of children under 1 year with congenital cleft upper lip observed a significant increase in IL-4 - 12.7 ± 1.57 pg / ml (P <0,001), (Table 1).

In children with congenital cleft palate this parameter was increased 7.7 times as compared with the control group (16,8 ± 1,59 pg / ml), (P <0,001). But the maximum value was found in children with cleft combined form (P <0,001).

In the group of children aged 1 to 3 years in congenital cleft upper lip tended to increase the level of IL-4 - 11,3 ± 1,56pg / ml, in patients with congenital cleft palate children observed a significant increase - 13.8 ± 1.39 pg / ml (P <0,05), and in children with comorbidity level of IL-4 was even higher - 16.7 ± 1.96 pg / ml (P <0,01).

Table 1: Level of IL -4 examined children, (M ± m, pg / ml).

groups	age groups		
	From 0 to 1 year	1 - 3 years	36 years
Control Group	2.18 ± 0.31	9.16 ± 0.82	6.35 ± 0.61
CCUL	12.7 ± 1.57 *	11.3 ± 1.56	9,5 ± 0,98 *
CCP	16.8 ± 1.59 *	13,8 ± 1,39 *	8.9 ± 0.9 *
CCULaP	22.6 ± 2.13 *	16,7 ± 1,96 *	14.3 ± 1.25 *

Note: * Values valid in relation to the control group (P <0,05-0,001)

For children aged 3 to 6 years, the level of IL-4 was significantly elevated in all forms of cleft, (P <0,05), but the maximum value of IL-4 in this age group was observed in congenital cleft lip and palate - 14,3 ± 1,25pg / ml, (P <0,05).

Thus, the level of anti-inflammatory cytokine IL-4 with congenital cleft lip and/ or palate in all age groups was higher. Perhaps this is due to the stimulation of eosinophils and monocytes. At this age, the frequency is observed respiratory diseases associated with allergy.

Significant importance is attached to IL-6, which promotes the early stages of hematopoiesis and osteoclastogenesis. It is synthesized in the culture of both stromal and osteoblastic cells in response to certain hormonal stimuli (PTH, calcitriol). IL-6 promotes bone resorption and increased osteoclastogenesis. An important role in the regulation of osteoclastogenesis play IL-2, MCP-1 and IL-4 inhibitors of bone resorption. From the analysis of the literature data It implies that IL-6 plays the role of growth factors and osteoclast precursors exerts indirect effects on bone resorption, while IL-2 stimulates the steps of osteoclast maturation.[5,6]

Analysis of the research results showed that the level of IL-6 in children under the age of 1 year with congenital cleft upper lip was significantly increased, (P <0,01) (Table 2). In children with congenital cleft palate levels of this cytokine is almost 3 times was above the reference value, (P <0,01). And in congenital cleft lip and palate, this figure was 3.7 times higher than control group values, (P <0,01). It should be noted that a

significant difference was observed with regard to the values of the group with congenital cleft lip and palate, and a group of children with congenital cleft lip (P<0,05).

Table 2: The level of IL -6 in the examinees, (M ± m, pg / ml).

Groups	age groups		
	From 0 to 1 year	1 - 3 years	36 years
Control Group	4.8 ± 0.43	6.07 ± 0.63	5.15 ± 0.5
CCUL	12,8 ± 1,43 *	5.84 ± 0.66	6.3 ± 0.74
CCP	14.3 ± 1.58 *	6.97 ± 0.73	8.5 ± 1.03 *
CCULaP	17,6 ± 1,9 * **	5.4 ± 0.57	7.8 ± 1.28 *

Note: * Values valid in relation to the control group
** Values are valid with respect to the group CCUP (P<0,05-0,001)

Analysis of the results in children aged 1 to 3 years showed that in all types of congenital cleft of IL-6 level was within the range of the control group. Thus, children with congenital cleft lip average level was -5.84 ± 0.66 pg / ml, in children with congenital cleft palate -6.97 ± 0.73 pg / ml and in children with comorbidity - 5, 4 ± 0,57 pg / ml.

With regard to children aged 3 to 6 years, the significant difference in the content of IL-6 has been in children with congenital cleft lip -8,5 ± 1,03 pg / ml, (P <0,05) and in children with congenital cleft lip and palate - 7.8 ± 1.28 pg / ml, (P <0,05).

Thus, IL-6 levels were dramatically increased in congenital clefts in children in the age aspect up to 1 year. Since the significance of IL-6 is given to stimulate the early stages of hematopoiesis, promoting bone resorption and increasedosteoclastogenesis, its elevated levels, possibly associated with impaired osteoclastogenesis stage in young children.

IL-18 is produced mainly by macrophages, including liver Kupffer cells and dendritic cells.[6] In addition, IL-18 mRNA was detected in human skeletal muscle cells, keratinocytes, hematopoietic myelomonocytic cell lines.[3] The fact that the expression of IL-18 gene as widely reported in various cell types, indicating the participation of this cytokine not only in the immune response, but also in the regulation of other physiological processes in different tissues and organs. IL-18 has pleiotropic effects on many types of cells and influences the secretion of various mediators of their functional orientation. There are data on both the pro- and anti-inflammatory IL-18 activity. IL-18 stimulates the production of proinflammatory cytokines such as IL-2, IL-6, IL-8,

In our studies, it was found that in the group of children under 1 year level of IL-18 was significantly increased for all types of congenital cleft, (Table 3). Thus, children with congenital cleft lip IL-18 level was 1.4 times higher than control group values - 263.2 ± 25.8 pg / ml, (P <0,05), and in children with congenital cleft palate this cytokine was higher in the control group values 1.75, (P <0,05). The maximum value of IL-18 was observed in congenital cleft lip and palate -515.3 ± 50.7 pg / ml, (P <0,01).

Analysis results of the study IL-18 levels in children in the age group 1-3 years showed that the maximum value of its observed in congenital cleft lip and palate - 1045.3 ± 86.2 pg / ml, (P <0,001). In children with congenital cleft palate level of IL-18 was 2.3 times higher than control group values - 689.7 ± 65.2 pg / ml, (P <0,01). A in children with congenital cleft lip content of IL-18 exceeded almost 2 times the value of control group - 586.3 ± 52.7 pg / ml, (P <0,01).

Table 3: The level of IL -18 in the examinees, (M ± m, pg / ml).

Groups	age groups		
	From 0 to 1 year	1 - 3 years	36 years
Control Group	193.5 ± 13.6	294.7 ± 16.7	217.4 ± 12.04
CCUL	263,2 ± 25,8 *	586,3 ± 52,7 *	398,2 ± 30,5 *
CCP	338,4 ± 37,18 *	689,7 ± 65,2 *	421,5 ± 49,6 *
CCULaP	515,3 ± 50,7 * **	1045,3 ± 86,2 * **	799,1 ± 62,5 * **

Note: * Values valid in relation to the control group
** Values are valid in relation to the group and CCP CCUP (P<0,05-0,001)

Data analysis in children aged 3 to 6 years also showed an increased level of IL-18 for all types of congenital cleft. In children with congenital cleft palate was increased almost 2-fold, (P<0,05). A children with comorbidity maxillofacial levels of this cytokine was increased 3.7 times, (P<0,001).

Thus, IL-18 levels in children with congenital cleft lip and / or palate was significantly increased in all age groups. Elevated levels of this cytokine is indicative of the influence of disturbances in the process of maturation of osteoclast function of immune cells, which contribute to increased synthesis of this cytokine.

As is known, IL-18 in a series of immunoregulatory mediators occupies a special position, since it is one of the key cytokines forming innate and acquired immune responses, differentiation and functional activity of macrophages, dendritic cells and T-lymphocytes.[2,3,4] Due to the presence of such diverse activities in this cytokine, he takes part not only in the defense reactions of the body, but also in the pathogenesis of many diseases associated with chronic inflammation and tissue destruction. Consequently, the level of IL-18 may be a predictor of the development of disturbances in the immune system in children with congenital cleft lip and / or palate.

Monocyte chemoattractant protein-1 (MCP-1) belongs to a large family of cytokines hemotoxic causing migration of leukocytes into the inflamed area. MCP-1 is widely involved in normophysiological (angiogenesis) and pathophysiological processes in the body.[4,6] The source of synthesis MCP-1 is a wide range of cells: fibroblasts, monocytes and macrophages, endothelial cells, leiomyocyte, cardiorabdomyocytes, cortical kidney epithelial cells, keratinocytes, epithelial cells line HEP-2 intestinal epithelial cells, osteoblasts, adipocytes, liver, chondrocytes, melanocytes mesotheliocytes, stromal cells bone marrow, astrocytes.[7,8]

In connection with the above, we have carried out a study on the level of MCP-1 in children with cleft lip and / or palate in the age aspect. As can be seen from Table 4, in children under 1 year, the level of this chemokine has been increased in all forms of cleft. Thus, in congenital cleft lip MCP-1 level was increased 1.36 times, (P<0,05). In congenital cleft lip MCP-1 level was even higher - (P<0,01). However, concomitant pathology, levels of this cytokine greater than the control group data in 3-fold, (P<0,001). It should be noted that the importance of MCP-1 in children with combined cleft was higher, not only the control group values, but also values of children with cleft lip (P<0,01) and cleft palate (P<0,05).

Table 4: MCP-1 level in the examinees, (M ± m, pg / ml).

groups	age groups		
	From 0 to 1 year	**1 - 3 years**	**36 years**
Control Group	223.4 ± 17.1	178.4 ± 15.6	148.5 ± 8.78
CCUL	305,4 ± 29,8 *	213.7 ± 21.3	273,6 ± 25,5 *
CCP	426,2 ± 41,1 *	378,5 ± 32,5 *	295,8 ± 27,6 *
CCULaP	679,1 ± 52,3 * **	566,4 ± 49,2 * **	367,1 ± 43,8 *

Note: * Values valid in relation to the control group
** Values are valid in relation to the group and CCP CCUP (P <0,05-0,001)

Analysis of the results of the study in children with different types of clefts in age from 1 year to 3 years showed that there was a significant increase in the level of MCP-1 in congenital cleft lip was observed only a tendency to increase, and in patients with cleft palate children, (P<0 , 01). And in children with congenital cleft lip and palate MCP-1 levels were above the reference value in 3.17 times, (P<0,001).

Results at the age of 3-6 years the level of MCP-1 studies in children also showed an increase in its pediatric patients. Thus, MCP-1 levels in children with congenital cleft lip was 1.84 times higher values of the control group (P<0,05), and in children with congenital cleft lips he averaged 295.8 ± 27.6 pg / mL, which is almost 2 times higher than the control values (P<0,01). In children with congenital cleft lip and palate levels of this cytokine was more than 2-fold higher than control values (P<0,01).

Thus, research age dynamics of the content of the pro- and anti-inflammatory cytokines in children with congenital cleft lip and / or palate (CCULaP) showed that in the age group up to 1 year with cleft lip and palate sharply increased levels of IL-4 and IL-6, and at children aged 3-6 years, increased levels of IL-18 and MCP-1, and in children aged 1 to 3 years, the level of IL-18 increased sharply.

Investigation of age dynamics of the content of the pro- and anti-inflammatory cytokines in children with congenital cleft palate showed a somewhat different pattern of change, is primarily to a sharp increase in IL-18 contents in children in the age range from 1 year to 3 years. The level of IL-4 was the most elevated in children the youngest of the group, while in children aged 1 to 3 years and in children under 6 years of the contents of this cytokine was the same. MCP-1 levels were similar in all patients children. Along with this, IL-6 levels were maximally increased in infants.

Analysis of the pro- and anti-inflammatory cytokines in children with congenital cleft lip and palate revealed the following features depending on the age range. The level of all investigated cytokines significantly different from the control group. Of all studied cytokines was most strongly increased content of anti-inflammatory cytokine IL-4 (10 times). IL-6 level was highest in children under

1 year, and IL-18 the highest rate was in children aged 3 to 6 years. The content of monocyte chemotactic protein 1 was increased in all children with a maximum value in children up to 3 years.

It should also take into account that IL-18 plays a central role among the many factors that stimulate excessive osteoclast activity, in connection with the than its lower level than MCP-1 may be an indication of significant bone remodeling disorders CCULaP with children of various age groups.

At the same time, set us characteristic CCULaP high level of production of anti-inflammatory IL-4, celebrated in different age groups of children surveyed, should also be considered a poor prognostic factor, since it is known that IL-4 inhibits the formation of osteoclasts and is a potent inhibitor of bone resorption.

Thus, it is shown pathogenetic role and diagnostic value of the studied cytokine (IL-4, IL-6, IL-18 and MCP-1) in children with congenital cleft lip and palate, the severity of which can be a criterion for the degree of violation remodeling process bone, that must be considered when carrying out surgical treatment in this group of children.

SUMMARY

In 210 children with congenital cleft lip and / or palate in the age aspect from 4 months to 6 years, were carried out to determine the level of pro- and anti-inflammatory cytokines. research results shows a pathogenetic role and diagnostic value of the studied cytokine (IL-4, IL-6, IL-18 and MCP-1) in children with congenital cleft lip and palate in age aspect, the severity of which can be a criterion for the degree of violation remodeling process bone, that must be considered when carrying out surgical treatment in this group of children.

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